

Version Number: 3	Research & Development Policy 151-02	Supersedes Document Dated: 3/2011
Effective Date: 03/12/12	STANDARD OPERATING PROCEDURES FOR HUMAN STUDIES RESEARCH	Expiration Date: 03/12/16

*Our mission is to care for our veterans with compassion and excellence.
Our vision is to be the health care provider of choice, achieving the highest quality in
health care delivery, education and research.*

I. PURPOSE

The purpose of this memorandum is to establish policies and procedures to protect the safety of human subjects who volunteer to participate in research protocols conducted under the auspices of the Research & Development (R&D) Service, as per Medical Center Memorandum No. 1, Section 4, R&D 151-01. These Policies and Procedures may be revised, subject to federal regulations, Federal-Wide Assurance documents, and the approval of the Institutional Official (Medical Center Director) and/or his or her designees (R & D Committee, Institutional Review Board (IRB)). Revisions and amendments may be made in the course of the year by the Chairperson, IRB or the Medical Center Director or the R & D Committee to reflect necessary changes in policies or procedures and will be presented to the IRB for review and ratification. These Policies and Procedures are available to all members of the IRB and to any researcher through the research webpage: <http://www.visn2.va.gov/research/syr/index.asp> or by contacting the IRB Office.

II. POLICIES & PROCEDURES

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DEFINITIONS: See R&D SOP 151-01 Appendix B.

A. RESPONSIBILITIES:

The Institutional Review Board (IRB) (OHRP IRB #00000658) serves, under the authority of Syracuse VA Medical Director and his designee, the R&D Committee, as the Institutional Review Board for Human Subject Research for the Syracuse VA Medical Center and its affiliated community based outpatient clinics (CBOCs), the Canandaigua VAMC and its affiliated CBOCs, the Bath VAMC and its affiliated CBOCs and the Central NY Research Corporation. In this capacity, the IRB has the responsibility for ensuring that research is conducted under the most rigorous ethical standards in order to assure the protection of the rights, welfare, and safety of human subjects.

Specifically, it is the responsibility of the IRB to review and approve, require modifications in, or disapprove all research proposals involving the use of human subjects. The IRB's reviews are for ethical appropriateness and compliance within the principles set forth by the Federal-Wide Assurances enacted between the United State Department of Health and Human Services (HHS) as represented by the Office for Human Research Protections (OHRP) and the Syracuse VA Medical Center (FWA # 00000117), the Canandaigua VAMC (FWA # 00000139), the Bath VAMC (FWA # 00002072) and the Central NY Research Corporation (FWA # 00001205). To carry out this responsibility and to ensure that the rights and welfare of human subjects are adequately protected, the IRB will be guided by the ethical principles of the Belmont Report and will implement the regulatory procedural standards as presented in the document entitled "Federal Policy for the Protection of Human Subjects" (FP), known as the "Common Rule," which represents a consolidation of related regulatory policies of all federal agencies, and which is mandated by the HHS under the document entitled "Protection of Human Research Subjects" Title 45 Code of Federal Regulations (CFR) Part 46 of the United States Department of Health and Human Services. In addition, the IRB review processes will conform to the regulatory requirements of the document entitled "Protection of Human Research Subjects" Title 38 Code of Federal Regulations (CFR) Part 16 of the United States Department of Veterans Affairs (DVA); the DVA document entitled "Requirements for the Protection of Human Subjects in Research," published as VHA Handbook 1200.05, October 15, 2010, which implements 38 CFR 16; the documents entitled "Protection of Human Subjects" 21 CFR 50; "Institutional Review Boards" 21 CFR 56; "Investigational Drugs" 21 CFR 312; "Investigational Devices" 21 CFR 812 of the United States Food & Drug Administration (FDA); and the HHS document entitled "Standards for Privacy of Individually Identifiable Health Information," also known as the Privacy Rule of the Health Insurance Portability and Accountability Act (HIPAA), Title 45 CFR, Part 160 and Subparts A and E of Part 164.

The provisions of these policies and procedures shall apply to all research involving human subjects that is conducted completely or partly in the Syracuse VA Medical Center and its affiliated CBOCs, the Canandaigua VAMC and its affiliated CBOCs, the Bath VAMC and its

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affiliated CBOCs, and the Central NY Research Corporation, and/or conducted in other VA and approved non-VA off-site locations and/or conducted by VA researchers from these institutions while on VA official duty time. The provisions also include research that is to take place elsewhere utilizing data collected on VA patients, research subjects, or staff of the Syracuse VA Medical Center and its affiliated CBOCs, the Canandaigua VAMC and its affiliated CBOCs, the Bath VAMC and its affiliated CBOCs, and the Central NY Research Corporation, including those data stored in any form on or off the premises of the Syracuse VA Medical Center and its affiliated CBOCs, the Canandaigua VAMC and its affiliated CBOCs, and the Central NY Research Corporation, with or without the involvement of staff of these institutions. The review process will be the same for all research involving human subjects, regardless of its source of funding and whether it is supported or otherwise subject to regulation by any Federal department or agency, sponsored by any other extramural entity, or initiated within the Syracuse VA Medical Center and its affiliated CBOCs, the Canandaigua VAMC and its affiliated CBOCs, the Bath VAMC and its affiliated CBOCs and the Central NY Research Corporation.

In order to approve research governed by this policy, the IRB will determine that all of the following requirements are satisfied.

1. **Is the Project Research?** The IRB's first responsibility is to determine whether or not the proposed project constitutes a research study (see subpar. 3jjj and 38 CFR 16.102(d)). If the project does not constitute research, the IRB has no responsibilities for review or approval beyond the determination that the project does not constitute research.
2. **Does the Research Involve Human Subjects?** If the project does constitute a research study, the IRB must determine whether or not it involves human subjects as defined in VHA Handbook 1200.05 and 38 CFR 16.102(f). (*See R&D Form Defining Human Subject Research*)
3. **Is the Human Research Project Exempt?** If the study constitutes research involving human subjects, then the IRB Chair or another IRB voting member designated by the IRB Chair must determine whether or not the study is exempt from IRB review. If the study is exempt from IRB review, the IRB does not have to approve it (see par. 16). (R&D SOP 151-08)
4. **Non-Exempt Research.** If a proposed human research study does not meet the criteria for exemption from IRB review, the study is considered "non-exempt," and the IRB must:
 - (a) Conduct initial review using a convened or expedited review procedure,
 - (b) Determine whether the research has satisfied all relevant criteria for approval, and
 - (c) Perform subsequent continuing review as appropriate.
5. **Scientific Review.** The IRB has been delegated by the R&D Committee to perform a

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comprehensive scientific review of the study.

6. Minimization of Risks: The IRB must determine that risks to human subjects are minimized (38 CFR 16.111(a)(1)) by using procedures that:

- (1) Are consistent with sound research design and which do not unnecessarily expose subjects to risk, and
- (2) Are already being performed on the subjects for diagnostic or treatment purposes, whenever appropriate.

NOTE: Consultation with subject matter experts or review by other committees or subcommittees (e.g., Biosafety or Radiation Safety) may be necessary to ensure risks to human subjects are minimized.

7. Risks and Benefits. The IRB must determine that risks to subjects are reasonable in relation to anticipated benefits, if any, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB needs to consider only those risks and benefits that may result from the research (as distinguished from risks and benefits the subjects would receive even if not participating in the research). The IRB is not to 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 (38 CFR 16.111(a)(2)).

(1) The IRB must ensure protocols with treatment or services that constitute “usual care” include a narrative section that clearly differentiates the research interventions from usual care, whether usual care is delivered to only some or to all research subjects (see subpar. 10g).

(2) In addition, the IRB must ensure the informed consent process clearly defines for the subject which potential risks are related to the research (38 CFR 16.116(a)(2) and, therefore, need to be discussed with the research team, versus those associated solely with usual care provided by the subject’s health care provider. The informed consent process is to include language advising subjects to review the risks of the latter with their health care providers.

(3) Should an IRB question a protocol’s characterization of “usual care,” its associated risks, or the person or entity responsible for specific aspects of “usual care,” the IRB is to seek clarification from the investigator and, if warranted, from qualified experts (38 CFR 16.107(f)). The IRB must document its determination(s) accordingly.

8. Equitable selection of subjects:

(1) That selection of subjects is equitable. In making this assessment the IRB takes into account the purposes of the research and the setting in which the research is to be conducted and it needs to be particularly cognizant of the special problems of research involving vulnerable populations, such as: children, prisoners, pregnant women, mentally-disabled persons, and economically or educationally disadvantaged persons (38 CFR 16.111(a)(3)).

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(2) If recruitment of non-Veterans is justified and appropriate.

9. Securing informed consent:

(1) Ensure that informed consent is obtained from each prospective subject or the subject's LAR in accordance with 38 CFR 16.116.

(2) Ensure the informed consent form includes all applicable elements.

(3) Ensure the informed consent form includes appropriate blocks for signatures and dates.

(4) Ensure the informed consent form is consistent with the protocol and, when relevant, with the HIPAA authorization.

(5) Determine that informed consent is appropriately documented, in accordance with, and to the extent required by 38 CFR 16.117 (38 CFR 16.111(a)(5)); VHA Handbook 1200.05 par. 33); 45 CFR 46 (DHHS) and 21 CFR 50 (FDA).

10. Monitoring safety: The IRB must determine, when appropriate, that the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects (38 CFR 16.111(a)(6)). The plan may include establishing a DMC as required by VA or DHHS, and a plan for reporting DMC findings to the IRB and the sponsor. For studies that do not have or are not required to have a DMC and are blinded, have multiple sites, enter vulnerable populations, or employ high-risk interventions, the IRB needs to carefully review the data and safety monitoring plan; it may suggest creation of a DMC.

NOTE: A sponsor (e.g., ORD or NIH) may require a DMC for a specific study. However, even if a sponsor does not require a DMC, an IRB may determine that a DMC must be established for that study.

11. Privacy and confidentiality: adequate provision, when appropriate, is made to protect the privacy of subjects and to maintain the confidentiality of the data.

12. Protection of vulnerable subjects: The IRB must assess the individuals or populations being recruited for potential vulnerability to coercion or undue influence, lack of decision-making capacity or increased susceptibility to harm from the research under review. **(See R&D SOP 151-06).** If vulnerability is determined to exist, the IRB must ensure that additional safeguards have been included in the study to protect the rights and welfare of these subjects (38 CFR 16.111(b)). In addition, research involving certain categories of subjects (e.g., pregnant women, prisoners, and children) must adhere to specific requirements.

13. Conflict of Interest: The IRB must ensure that steps to manage, reduce, or eliminate potential, actual, or perceived conflicts of interest related to all aspects of the research (financial, role (investigator-patient relationships), and other professional, institutional, or personal roles) have been taken. **(See R&D SOP 151-05)**

14. Investigator's Educational Requirements and Certification: will determine that the PI,

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all other investigators, and all personnel involved in the conduct of the human subject research have met all current educational requirements for the protection of human subjects as mandated by the facility's Research Education SOP 151-24, Federal Wide Assurance, VA ORD, funding institutions, and applicable OHRP requirements. The IRB will also determine that the investigators(s), and all study-associated personnel are qualified through education, training and experience to conduct the research.

B. OVERVIEW OF IRB:

1. Authority.

The authority conveyed to the IRB includes the following:

- Review all research projects involving human subjects, before the involvement of human subjects begins;
- Require from investigators revisions in research protocols, informed consent documents, and privacy/confidentiality documents, as a condition for initial or continuing approval;
- Approve new research projects, and continuation of previously approved projects;
- Disapprove the initiation of a new research project;
- Monitor the activities in approved projects, in any way deemed necessary, including regularly scheduled continuing review at least every twelve months, and verification of compliance with approved research protocols and informed consent procedures;
- Ensure prompt reporting to the IRB of any planned changes in approved projects, and that no material changes occur without prior approval by the IRB;
- Ensure prompt reporting to the IRB of any adverse events and/or serious adverse events occurring in approved projects, or in other projects related in context to the approved projects;
- Suspend or terminate a previously approved project; and
- Review and monitor the use of test articles (investigational drugs, and biologicals) for the purpose of treatment of serious or life-threatening illnesses.
- IRB has authority to observe, or have a third party observe, the consent process and the research (38 CFR 16.109(e)).

Research that has been approved by the IRB is subject to further appropriate review and approval or disapproval by officials (e.g., the facility Director) and other committees (e.g., the R&D Committee). However, officials or committees cannot approve the research if it has been disapproved by the facility's IRB of record (e.g., the VA facility Director cannot approve a study that has been disapproved by IRB) (38 CFR 16.112).

2. IRB/Investigator Conflicts of Interest: are managed as defined in R&D SOP 151-05

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3. Schedule of IRB Meetings.

The IRB meets on the fourth non-holiday Monday of each month, although the actual meeting dates may be moved forward or backward depending upon IRB needs and availability of voting membership. The R&D Committee meets on the second non-holiday Monday of each month. If there is no IRB business that needs to be dealt with, the regularly scheduled IRB meeting during the month of either July or August may be canceled due to vacation schedules and the resulting difficulty in obtaining a quorum. However, additional IRB meetings may be called at any time by the Chair to make up for missed meetings and to address other business that must be dealt with before the next regularly scheduled meeting. Although not a regular practice, meetings via teleconference or videoconference may be held between scheduled IRB meetings to deal with special emergency circumstances such as rapid review of a Treatment IND proposal using an experimental drug for compassionate treatment of a VA patient. Such teleconference or videoconference meetings shall be considered to have the same authority to review and vote upon motions as regularly convened meetings. As with regularly scheduled meetings, members will have received all pertinent material prior to the telephone or video meeting and will be able to actively and equally participate in all discussion of all protocols. Minutes of teleconference or videoconference meetings will clearly document that these two conditions have been satisfied, in addition to the usual regulatory requirements.

4. Membership of IRB.

a) Composition and Selection of IRB Members. The IRB will be sufficiently qualified through the experience and expertise of its members and the diversity of the members' backgrounds, including diverse racial and cultural backgrounds of members 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.

IRB membership will have at least 5 members and conform to the regulations of the DVA, DHHS and the FDA. Membership will include personnel from the VA as well as at least one member who is not otherwise affiliated with the VA. In addition, membership will include both men and women without regard to race or ethnicity. Further, both clinically and research oriented M.D.'s and Ph.D.'s, R.N.'s, and other appropriate health care professionals in a variety of disciplines will be appointed to review the various types of proposed research most commonly submitted to the IRB. At least 2 scientific members will be from behavioral science areas and at least 2 members will be medical doctors. At least 1 member will have primary concerns in non-scientific areas and at least 1 member will be an unaffiliated community member such as a clergy person, an attorney, or a veteran who is an active member of a veterans' organization or provides services for and/or advocates on behalf of the veteran research subjects. (Note that the unaffiliated member, the member representing the general perspective of subjects, and the non-scientific member may be the same person or they may be represented by two or three different persons). Finally, to help coordinate activities with research affiliates, at least one member will be a representative from the Canandaigua VAMC and one member from the Bath VAMC.

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To be effective and efficient in its operations, and to be responsive to the needs of the research community it serves, in its discretion, the IRB may increase, above the Federally mandated minimum, the number of its members in any category. In its discretion, the IRB may also reduce its membership, as long as the membership conforms to the Federally mandated minimum number and composition. The IRB membership will determine the scope of expertise of its members, to assure appropriate review of the types of applications it receives.

Members of the IRB are appointed by the Medical Center Director for a period of 3 years and may be re-appointed indefinitely. The IRB Chair is appointed by the Medical Center Director for a term of 1 year and may be re-appointed indefinitely.

Alternate IRB members may be used if they are formally appointed as alternates. The alternate member's qualifications shall be comparable to those of the primary member to be replaced. Alternate members will have voting rights, except that they may not vote at meetings attended by their respective regular members. The procedure for appointment of an alternate member will be the same as that of a regular voting IRB member. When an alternate member replaces the primary member in a meeting, the alternate member shall have received and reviewed the same material that the primary member would have received. The IRB roster shall identify the primary member(s) for whom each alternate member may substitute.

If an IRB member resigns or is no longer able to serve before completion of a 3-year term or if an IRB member leaves his/her current position or is no longer able to serve, the R&D Committee will be notified immediately of the membership opening and will seek, nominate and recommend appropriate replacements to the Medical Center Director as soon as possible.

To minimize conflicts of interest with their roles as officers of the affiliated Central New York Research Corporation, the Medical Center Director, Chief of Staff, Associate Chief of Staff (ACOS) for R&D, and Administrative Officer, R&D Service, may only serve as non-voting ex-officio members of the IRB.

The IRB defers to another meeting of IRB, or obtains consultation if there is not at least one person on the IRB with appropriate scientific expertise or other expertise or knowledge to conduct an in-depth review of the protocol.

Additional non-voting ex-officio members and non-voting ad hoc consultants may be added by the IRB as needed for dealing with specific issues or reviews that require additional expertise. Ad hoc consultants with appropriate expertise are identified and selected from among VA physicians not associated with protocols or issues under review, from among physicians at our academic affiliate, and from among VA content experts for non-medical/scientific issues (e.g., VA Chaplain, VA Attorney) by the IRB Chair. Ad hoc consultants do not have a vote, but may participate in the review of IRB issues by attending meetings in person, by teleconference, by videoconference, or by submitting written reports of their deliberations. All ad hoc consultants

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are subject to the same conflict of interest policies as IRB members.

A resume for each IRB member will be maintained in the IRB Office. A record of the names, degrees, qualifications, terms, affiliation, and voting status of the members of the IRB and alternate members will be maintained in the IRB administrative office (aka membership roster). Ex-officio members who attend meetings on a regular basis will also be included in this record. New appointments, dismissals, termination of appointments, and withdrawals of members will be noted at the monthly meeting when they occur. The appropriate regulatory agencies will be apprised of changes in committee membership, if any, at least annually. IRB Membership Rosters (current and historical) are available from the IRB Office.

b. Responsibilities of Individual IRB Members. By accepting the Director's nomination to the IRB, each IRB member is responsible for the following:

- (1) to attend each IRB meeting;
- (2) to review all materials and be prepared to discuss each agenda item;
- (3) to use all of one's area of expertise;
- (4) to consider the approval criteria offered in the regulations and the Belmont Report for each agenda item, and if assigned as a proposal's in-depth reviewer, to complete, sign and return all IRB reviewer forms;
- (5) to maintain confidentiality regarding any information contained in any review;
- (6) to reveal any potential conflict of interest to the IRB Chair as soon as it is recognized;
- (7) to provide the longest possible notice of inability to attend an IRB meeting;
- (8) to be familiar with these operating procedures and all attachments to them; and,
- (9) to complete required IRB training prior to active membership on the IRB.

The Medical Center Director is responsible for suspending or terminating the IRB membership of any individuals who are not fulfilling their member responsibilities or obligations.

c. Privacy Officer (PO) and Information Security Officer (ISO): (Non-voting ex-officio members) The PO and the ISO are responsible for:

(1) Ensuring the proposed research complies with all applicable local, VA and other Federal requirements for privacy and confidentiality, and for information security, respectively, by identifying, addressing, and mitigating potential concerns about proposed research studies, and by serving in an advisory capacity to the IRB Committee as a nonvoting member.

(2) Reviewing the proposed study protocol and any other relevant materials submitted with the IRB application.

***NOTE:** It is not sufficient for the Privacy Officer or ISO to review a checklist completed by the investigator, and not the study protocol and related materials themselves. To facilitate the*

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review of the proposal by the Privacy Officer and the ISO, the investigator must either dedicate specific sections of the protocol to privacy and information security, respectively, or the investigator must develop an additional document that specifically addresses all privacy and information security issues in the proposal, and that additional document will become part of the IRB protocol file.

(3) Completing their respective reviews of the proposed research and informing IRB of all their findings related to privacy and confidentiality, and to information security, respectively.

NOTE: *They are not responsible for approving or disapproving a study, nor do they have the authority to prevent or delay IRB approval of a study. The IRB is responsible for approving all non-exempt human research studies. Exempt studies should be approved in accordance with VHA Handbook 1200.01.*

(4) Identifying deficiencies in their respective reviews of the proposed research, and making recommendations to the investigator of options available to correct the deficiencies.

(5) Following up with the investigator, in a timely manner, to ensure the proposed research is in compliance with relevant privacy and confidentiality, and information security requirements, respectively, before the investigator initiates the study.

(6) Providing summary reports of their review and assessment of each study according to the requirements of this paragraph. The summary report must clearly:

- (a) Indicate either that all applicable local, VA and other Federal requirements for privacy and confidentiality, and for information security, respectively, have been met, or
- (b) Identify specific deficiencies and suggest available options for correcting those deficiencies.

(7) Providing their summary reports on each study to the IRB staff (whether VA or affiliate IRB) within a time frame that does not prolong the study approval process. They must provide their summary reports prior to, or at, the convened IRB meeting at which the study is reviewed or, in the case of expedited review, prior to, the IRB approval determination of the IRB Chair, or designee. For exempt studies, they must submit their summary reports to the ACOS for R&D, and ensure the study is in compliance before the study is initiated.

(8) Providing their final reports on each study to the IRB staff in a timely manner.

5. IRB Chairperson.

The Syracuse VAMC Medical Director, following recommendations submitted by the R&D Committee, appoints the Chairperson of the IRB. The Chair of a VA IRB must be a paid VA employee (i.e., not have a WOC or IPA appointment at VA). There may be one IRB Chair, Co-

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chairs, or a Chair and a Vice Chair. Each is a voting member of IRB. The Chair and, when applicable, the Co-chair, are appointed by the Institutional Official (IO) for a term of up to 1 year, and may be re-appointed after each year indefinitely.

6. Requirements for a Quorum.

Quorum. Except when an expedited review procedure is used (see par. 21 and 38 CFR 16.110), a convened meeting at which a majority of the voting members of the IRB are present (i.e., a quorum) is required for IRB to conduct any business including, but not limited to, voting on actions, and reviewing and approving research studies. The quorum must include at least one voting member whose is unaffiliated, one member representing the general perspective of subject and one member who's primary concerns are in non-scientific areas (Note that the unaffiliated member, the member representing the general perspective of subjects, and the non-scientific member may be the same person or they may be represented by two or three different persons.) (38 CFR 16.108(b)).

If research involving an FDA-regulated is article is involved, a licensed physician must be included in the quorum. Members who arrive late or leave early will be counted towards the quorum only when they are present at the meeting.

Whenever a research project application is being reviewed in which a member of the IRB may have a conflict of interest, that member will leave the site of the IRB meeting for the duration of the review of that application, will not participate in the discussions in any way, will not vote on the application, and will not count towards the required membership for a quorum on that application. Alternate members will be included in determining or establishing quorum at IRB meetings, when the respective regular members are absent, but not when they are present. It is acceptable for a member to attend a meeting via a teleconference or videoconference if that member received all pertinent materials in advance when other members received their materials and if that member is able to actively and equally participate in all discussions of all protocols. Minutes of meetings will list the names of any members who arrive late and/or leave early or who attended via telephone or videoconference. In addition, the IRB minutes shall document when an alternate member replaces a primary member. For special ad hoc meetings, as with regular meetings, a quorum will consist of a majority of the total voting membership, including at least one member whose primary concerns are in non-scientific areas.

The Research Administrative Staff present at the IRB Meeting will determine when quorum is established through documentation on the meeting sign-in list (based on the IRB Roster). They staff person(s) will notify the IRB Chairperson when quorum has been met or if at any time quorum has been lost due to recusal, excusal or absence of IRB voting members.

Lack of a Quorum. If the required number and type of voting members are not present at any point during a meeting, a quorum must be restored before any discussion of, or action on, issues requiring a vote may occur.

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7. Resource Persons for IRB.

Any questions regarding IRB can be directed to:

Sven K. Ljaamo, MD, MPH., IRB Chairperson, ext. 53540
 Andrea L. Hahn, IRB Administrator, ext. 53607.
 Deborah Collins, Administrative Officer for Research Service, ext. 54870
 Bernadette Kalman, MD, Associate Chief of Staff for R&D, ext 52471

C. RESEARCH SUBJECTS:

1. Recruitment, solicitation, and payment of research subjects.

The facility Director is responsible for ensuring that recruiting documents, flyers, and advertisements for non-VA research are not posted within or on the premises of a VA facility. Posting of such documents may give the Veteran or visitors to the VA facility the impression that the non-VA study is VA-approved research, the VA supports or endorses the research, or that VA will pay for the research expenses that are incurred. General guidance may be posted within VA indicating that Veterans may speak with their health care providers if they wish to participate in research and that information on clinical trials is available at: <http://clinicaltrials.gov>. It is also **not** appropriate to distribute an email for recruiting subjects to non-VA studies.

The IRB requires that proposals submitted by PI(s) contain information about the subjects to be involved directly in the research in order to determine whether the subjects are suitable for the type of research, are recruited in reasonable numbers, participate in the study long enough to obtain valid new knowledge, have been selected equitably, and how vulnerable or prone to coercion they may be. "Equity" in recruitment of human research subjects is mandated by Federal regulations. The conventional understanding of equity is the assurance that the prevalence of age ranges, gender, ethnic groups and racial groups found within the communities are fairly represented among the subjects in the study, unless the study focuses on a specific subset of the community, for justifiable reasons. *If a project includes a study population in which women and minorities, etc., are not appropriately represented or excludes any class of persons who may benefit from the research, the investigator must provide a clear compelling scientific and ethical rationale for their exclusion or inadequate representation.* The IRB will also review the manner in which subjects are recruited (e.g., letter, phone solicitation, through primary care providers, signage in clinics, patient records, etc.) in order to evaluate the equity of selection, maintain patient privacy and minimize possible coercion or undue influence upon prospective subjects. All VA patients must be reassured during the consent/authorization for release of protected health information (PHI) process that no benefits to which they are otherwise entitled, and no care or concern on the part of the health care providers, will be jeopardized by a decision not to participate in research/authorize release of PHI.

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2. Who May Be Recruited. VA research needs to be relevant to Veterans or active duty military personnel. The investigator must justify including non-Veterans in a VA research protocol, and the IRB must review the justification for inclusion of non-Veterans and specifically approve entering non-Veterans into the study before any non-Veterans can be recruited. The IRB must appropriately document in the IRB minutes or IRB protocol file its determinations regarding participation of non-Veterans in the study.

a. **Outpatient Care for Research Purposes.** Any person who is a bona fide volunteer may be furnished outpatient treatment when the treatment to be rendered is part of an approved VA research study and there are insufficient Veteran patients suitable for the study (38 CFR 17.92).

b. **Hospital Care for Research Purposes.** Any person who is a bona fide volunteer may be admitted to a VA hospital when the treatment to be rendered is part of an approved VA research study and there are insufficient Veteran patients suitable for the study (38 CFR 17.45).

c. **Other Research.** Non-Veterans may be entered into an approved VA research study when the investigator can present a compelling argument to the IRB for the inclusion of non-Veterans (e.g., insufficient number of Veterans; survey of VA employees; study of active duty military; study involving Veterans' family members), and the research is relevant to the care of Veterans or active duty military personnel.

When non-veterans and employees are used as research subjects, it may be expected that research funds reimburse the medical care appropriation for any hospitalization and for any outpatient visit. The budget for the project shall reflect these expenses.

3. Solicitations for Participation. It is an acceptable and often necessary practice to publicly solicit human subjects for participation in research projects. Such solicitations may include flyers, posters, radio or television advertisements, or public service announcements, newspaper advertisements or similar items. However, such solicitation must be conducted with the dignity and tact that such activity deserves and in accordance with applicable regulations, policies and law. Accordingly, all advertisements to recruit subjects should be limited to: 1) the name and address of the clinical investigator; 2) the purpose of the research, and, in summary form, the eligibility criteria that will be used to admit subjects into the study; 3) a straightforward and truthful description of the incentives to the subject for participation in the study (e.g., payments or free treatment); and 4) the location of the research and the person to contact for further information. If a study involves investigational drugs, no claims may be made, either explicitly or implicitly, that the drug is safe or effective for the purposes under investigation, or that the drug is in any way equivalent or superior to any other drug. Such representation would not only be misleading to subjects, but would also violate FDA regulations concerning the promotion of investigational drugs.

Investigators are responsible for preparing solicitations and submitting them to the IRB for review and approval before they may be used. The IRB Chairperson and, if needed, the Syracuse

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VAMC Public Affairs Office, will provide initial assistance and review of direct patient solicitations to assure they are suitable for public display, contain non-technical language, are appropriate for a lay audience, meet applicable regulations, and are acceptable to the Chief of Staff (COS) and Medical Center Director. Solicitation requests to professional staff for referrals of patients to research projects also require IRB review and approval with preliminary review by the IRB Chairman and assistance of the Public Affairs Office, if needed, to assure that they are suitable for public display, are appropriate for a professional audience, and are acceptable to the COS and Medical Center Director.

4. Payment for Subjects. VA policy prohibits paying subjects in research when the research is an integral part of a subject's medical care and when it makes no special demands on the subject beyond those of medical care. The amount of payment and the proposed method and timing of disbursement may neither be coercive nor present undue influence. Credit for payment is to be accrued as the study progressed and not contingent upon the participant completing the entire study. Any amount paid as a bonus for completion must be reasonable and not so large as to unduly induce participants to stay in the study when they would otherwise have withdrawn.

a. Payments to subjects may be permitted, with IRB approval, in the following circumstances:

- (1) **No Direct Subject Benefit.** When the study to be performed is not directly intended to enhance the diagnosis or treatment of the medical condition for which the volunteer subject is being treated, and when the standard of practice in affiliated non-VA institutions is to pay subjects in this situation.
- (2) **Others Being Paid.** In multi-institutional studies, when human subjects at a collaborating non-VA institution are to be paid for the same participation in the same study at the same rate proposed.
- (3) **Comparable Situations.** In other comparable situations in which, in the opinion of the IRB, payment of subjects is appropriate.
- (4) **Transportation Expenses.** When transportation expenses are incurred by the subject that would not be incurred in the normal course of receiving treatment and which are not reimbursed by any other mechanism.

The IRB must review all proposals for payment of subjects to ensure conformity with VA policies. The facility research office is responsible for ensuring that IRB-approved payment to subjects is made from a VA approved funding source for research activities. Any payments designed to accelerate recruitment that are tied to the rate or timing of enrollment are prohibited.

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b. Instructions to Investigators. Prospective investigators who wish to pay research subjects must in their proposal:

- (1) Substantiate that proposed payments are reasonable and commensurate with the expected contributions of the subject;
- (2) State the terms of the subject participation agreement and the amount of payment in the informed consent document; and
- (3) Substantiate that subject payments are fair and appropriate, and that they do not constitute (or appear to constitute) undue pressure or influence on the prospective research subjects to volunteer for, or to continue to participate in, the research study; and that the payments do not constitute (or appear to constitute) coercion to participate in, or continue to participate in, the research study.

c. Payments for Recruitment by VA/Non-VA Staff. While subjects may receive payments, professional staff, residents, medical students, nurses, research technicians and coordinators and all other VA and Central NY Research Corporation employees are strictly prohibited from offering or receiving any “finder’s fee” or other inducement, in cash or in kind, for the purpose of referring patients as candidates for participation in research.

5. Vulnerable Populations.

a. VA Requirements. Whenever VA has more stringent requirements than DHHS for protection of vulnerable individuals or vulnerable populations as research subjects, all VA requirements must be met.

b. Documentation of Vulnerability. Where relevant, the IRB needs to document why it considers an individual or population to be vulnerable, and that adequate safeguards have been included in the study to protect the rights and welfare of subjects who are likely to be vulnerable. Individuals or populations that may be temporarily or permanently vulnerable include, but are not limited to, those who:

- (1) Are susceptible to coercion or undue influence (e.g., the homeless, prisoners, students, patients with limited or no treatment options, socially and economically disadvantaged).
- (2) Lack comprehension of the research and its potential risks (e.g., educationally disadvantaged, dementia, schizophrenia, depression) (see par. 49).
- (3) Have increased susceptibility to harm from the procedures of the specific study under review (e.g., individuals who would have to answer study survey questions about their sexual assault).
- (4) Are at risk for economic, social, or legal consequences from the study (e.g., individuals who would have to answer study survey questions about their drug use or HIV status).

c. Populations Considered to be Categorically Vulnerable. This subparagraph defines populations that are considered categorically vulnerable and specifies VA requirements for the

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inclusion of any of these categories of subjects in research. While all protocols need to be assessed for vulnerability of subjects within the context of the specific protocol (see subpar. 17h), the populations named in this subparagraph must always have the additional protections specified in this paragraph applied. VA considers the following populations to be categorically vulnerable:

- (1) **Fetuses.** Research in which the focus is either a fetus, or human fetal tissue, in-utero or ex-utero (or uses human fetal tissue), must not be conducted by VA investigators while on official duty, or at VA facilities, or at VA approved off-site facilities.
- (2) **Neonates.** Research related to neonates including, but not limited to, observational or interventional research, must not be conducted by VA investigators while on official duty, or at VA facilities, or at VA approved off-site facilities.
- (3) **Pregnant Women.** See paragraph e.
- (4) **Prisoners.** See paragraph f.
- (5) **Children.** See paragraph g.
- (6) **Subjects who Lack Decision-making Capacity.** See R&D SOP 151-06

d. In Vitro Fertilization. Research related to in vitro fertilization is not to be conducted by VA investigators while on official duty, or at VA facilities, or at VA-approved off-site facilities.

e. Research Involving Pregnant Women

This paragraph applies to women who are pregnant at the time they are entered into a study. It does not preclude entering women of child bearing potential into studies including studies whose interventions include FDA's Categories for Drug Use in Pregnancy's Category C drugs. Women of child bearing potential may not be entered into studies involving the use of FDA Categories for Drug Use in Pregnancy's Category D or X drugs unless a waiver is obtained from the CRADO. Pregnant women may be the focus of the research if all of the following conditions are met (45 CFR 46.204):

(1) **Prior Studies Have Been Performed.** Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses (45 CFR 46.204(a)).

(2) **Selection of Participants:** Adequate consideration has been given to the manner in which potential subjects are going to be selected.

(3) **Prospect of Direct Benefit.** The purpose of the activity is to meet the health needs of the mother or the particular fetus. The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means (45 CFR 46.204(b)).

(4) **Minimization of Risks.** Any risk is the least possible for achieving the objectives of the research (45 CFR 46.204(c)).

(a) One of the following is true:

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- The fetus is placed at risk only to the minimum extent necessary to meet the health care needs of the mother.
- The risk to the fetus is minimal.

(5) **Monitoring Risks.** Adequate provision has been made to monitor the risks to the subject and the fetus.

(6) **Informed Consent.** If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, the pregnant woman's informed consent is obtained in accord with the informed consent provisions of 38 CFR 16.116 (see pars. 30-35 and 45 CFR 46.204(d)).

(a) Consent is obtained from the mother and father, except that the father's consent need not be secured if:

- The purpose of the activity is to meet the health needs of the mother.
- His identity or whereabouts cannot reasonably be ascertained.
- He is not reasonably available.
- The pregnancy resulted from rape.

(b) Adequate provision has been made to monitor the actual consent process by procedures such as:

- Overseeing the process by which the consent of individuals is obtained either by: Approving enrollment of each individual or Verifying, perhaps through sampling, that approved procedures for enrollment of individuals into the activity are being followed.
- There should be adequate monitoring the progress of the activity and intervening, as necessary, through such steps as visits to the activity site and continuing evaluation to determine if any unanticipated risks have arisen.

(7) **Impact on Fetus.** Each individual providing informed consent, under subparagraph 46e, is fully informed regarding the reasonably foreseeable impact of the research on the fetus (45 CFR 46.204(f)).

(8) **No Inducements to Terminate Pregnancy.** No inducements, monetary or otherwise, are to be offered to terminate a pregnancy (45 CFR 46.204 (h)).

(9) **Decisions to Terminate Pregnancy.** Individuals engaged in the research have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy (45 CFR 46.204(i)).

(10) **Determining Viability of Fetus.** Individuals engaged in the research have no part in determining the viability of a fetus (45 CFR 46.204 (j)).

f. Research Involving Prisoners

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(1) **Vulnerable Population.** Prisoners are considered a vulnerable population and may be under constraints because of their incarceration which could affect their ability to make a truly voluntary and uncoerced decision whether or not to participate as subjects in research (45 CFR 46.302).

(2) **Waiver From CRADO.** Research involving prisoners cannot be conducted by VA investigators while on official VA duty, using VA resources, completely or partially in a VA facility or at a VA-approved off-site facility unless a waiver has been granted by the CRADO. If such a waiver is granted by the CRADO, the research must be in accordance with applicable Federal regulations pertaining to prisoners as research subjects (see 45 CFR 46, Subpart C 46.301–46.306, Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects). **NOTE:** *Requirements for requesting a waiver may be obtained by contacting ORD.*

(3) **Incarceration During a Study.** If a subject becomes incarcerated during the course of a study:

- (a) Investigators must notify the IRB as soon as they become aware that the subject has been incarcerated.
- (b) The investigator must make a determination as to whether or not it is the best interests of the subject to remain in the study, or if the subject can be safely withdrawn from the study.
- (c) If the investigator determines it is in the best interest of the subject to remain in the study, the subject's continued participation in the study is contingent on the IRB's reviewing and approving such participation. The IRB approval must comply with 45 CFR 46.301-306.
- (d) After IRB and other relevant approvals (e.g., from the penal system) for the incarcerated subject's continued participation in the study have been obtained, a waiver must also be obtained from the CRADO.
- (e) The investigator must comply with all applicable requirements including, but not limited to, applicable court, penal system, and local, VA, and other Federal requirements.

g. Research Involving Children

(1) **Waiver From CRADO.** VA is authorized to care for Veterans and to conduct research that supports the mission of VHA and that enhances the quality of health care delivery to Veterans. Therefore, research involving children cannot be conducted by VA investigators while on official VA duty, using VA resources, completely or partially in a VA facility or at a VA-approved off-site facility unless a waiver has been granted by the CRADO. **NOTE:** *For purposes of this Handbook, research involving biological specimens or data obtained from children is considered to be research involving children.*

(2) **Criteria for Waiver.** Prior to requesting a waiver, the following criteria must be met:

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- (a) The study represents no greater than minimal risk as determined by the IRB.
- (b) The study meets all requirements in 45 CFR 46, Subpart D, Additional Protections for Children Involved as Subjects in Research, Sections 46.401 through 46.404, and 46.408.
- (c) The IRB reviewing the study has appropriate membership to represent children's interests and pediatric expertise.
- (d) The IRB reviewing the study has specific SOPs regarding children in research.
- (e) The VA facility Director certifies that the facility is able to respond to pediatric emergencies if the study includes interactions with children at the VA facility.
- (f) If the sponsor of the research is not VA, the facility Director makes certain that the sponsor of the research has procured appropriate liability insurance.

(3) **Waiver Application.** To request a waiver, the following information must be submitted to ORD for each protocol:

- (a) A cover letter signed by the VA facility Director that contains the following information:
 - (1) Certification by the VA facility Director that the facility is able to respond to pediatric emergencies if the study includes an interaction with children at the VA facility.
 - (2) Any additional safeguards that have been incorporated into the clinical site where children will be studied.
 - (3) Information on the study's funding source and on liability coverage if the sponsor is not VA.
 - (4) Certification that the IRB has determined the study to be of no greater than minimal risk and has approved the study.
 - (5) A statement that the required elements of 45 CFR 46 Subpart D have been met.
 - (6) A description of the relevance to Veterans' health of both the study and the inclusion of children in the study.
 - (7) A copy of the study protocol, the informed consent form, the assent document, and HIPAA authorization. The informed consent document signed by the parent or guardian is the vehicle for parent or guardian permission. Provisions for permission by parents or guardians must be documented in accordance with and to the extent required by 38 CFR 16.117.
 - (8) Minutes of the IRB meeting approving the study. The IRB minutes need to reflect the discussion regarding level of risk, the informed consent and assent forms, the investigators' qualifications to conduct research involving children, and any additional safeguards incorporated into the protocol.
 - (9) If the study involves biological specimens or data collected from children, in addition to the preceding requirements, the following must be submitted:
 - a. A discussion of how the biological specimens or data were, or will be, obtained and under what consents or authorization.
 - b. If the biological specimens or data were, or will be, collected for research purposes, the IRB approval, the informed consent form, and the HIPAA

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authorization for the research.

- c. If biological specimens or data were, or will be, collected from an international site, a waiver from the CRADO for international research.
- d. Plans for future use of biological specimens or data.

6. Issues of privacy and confidentiality. The IRB must determine, when appropriate, that there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data (38 CFR 16.111(a)(7)). Such provisions must take into consideration the requirements of Standards for Privacy of Individually-Identifiable Health Information (HIPAA Privacy Rule), 45 CFR 160 and 164, and other laws regarding protection and use of Veterans' information, including the Privacy Act of 1974, 5 U.S.C. 552a; VA Claims Confidentiality Statute, 38 U.S.C. 5701; Confidentiality of Drug Abuse, Alcoholism and Alcohol Abuse, Infection with Human Immunodeficiency Virus (HIV), and Sickle Cell Anemia Medical Records, 38 U.S.C 7332; and Confidentiality of Healthcare Quality Assurance Review Records, 38 U.S.C 5705. An IRB does not have the authority to approve the HIPAA authorization unless it is incorporated into the informed consent form; however, VHA Handbook 1200.05 requires the HIPAA authorization and informed consent form to be two separate documents.

a. Recruitment of Subjects for Prospective Research Studies. The IRB does not allow recruitment procedures that involve a person (physician/caregiver, relative, etc.) providing protected health information about another individual (i.e., potential subject) without first obtaining waiver of Authorization or a valid signed Authorization from that individual for the use or disclosure of such information. The IRB recommends that investigators perform recruitment of potential subjects using IRB-approved flyers, advertisements or mailers. Such information might also be sent to other VA physicians/caregiver/staff for use in informing their patients of available studies. The potential subjects may then take an active role in expressing their interest in study participation by contacting the investigator directly. If a healthcare professional intends to disclose the patient's identity or any other PHI to a third party for recruitment purposes, either written Authorization or an IRB waiver of Authorization is required.

Using VA medical records and medical databases as a method to recruit subjects may be allowable, subject to conditions and IRB approval (see SECTION E.2.g.), as part of the HIPAA Privacy Rule (45CFR 164.512(i)(1)(ii)). However, even when record/data base review is permitted for recruitment, the IRB does not permit investigators (or their research staff) to personally contact potential subjects unless the researcher is also the subject's treating physician. If the investigator plans to recruit other physician's patients, the following procedures must be maintained:

- (1) The investigator must obtain permission from the patient's physician and provide the physician with IRB-approved study information (e.g., study abstract, letters, flyers, etc.).
- (2) The primary care physician, either personally (e.g., during a regularly scheduled appointment) or via mail, can inform the patient of the availability of the study and allow

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the patient to indicate whether he/she is interested in participating in the study and/or receiving further information. If so indicated, the investigator may be asked to contact the patient or, alternatively, the physician/caregiver can have the patient contact the investigator. An Authorization for release of PHI can be provided at this time to allow the investigator to access and use medically related information. The requirement for primary care physician contact with patients may be waived for minimum risk studies that qualify for waiver of written informed consent. The precise method of contact must be pre-approved by the IRB.

b. Use of Medical Records for Research. According to VA Medical Center policy, accessing electronic medical records is based on the “need to know” principle. A Department official or employee may have access to sensitive information in VA computer systems and storage media only when the official or employee needs access to that information in order to perform an assigned task or duty within the official responsibilities of the individual. All individuals who use or gain access to VA information or sensitive information must adhere to VHA and VISN 2 Network policies to include protection of individual user accounts, patient confidentiality, access to sensitive data and appropriate use of the internet and electronic mail. All individuals who have access to sensitive areas are responsible for: 1) accessing only data for which they have authorized privileges, and 2) maintaining confidentiality of sensitive data or information. According to Network policy, patient medical records, regardless of medium, will be preserved, and the information contained therein will not be accessible to or discussed with any unauthorized persons. Information that is available through the Computerized Patient Record System (CPRS), Veterans Integrated Systems Technical Architecture (VISTA) and Automated Data Processing System (ADP) is to be used by authorized personnel for official purposes only and will be treated with the same degree of confidentiality as information from the medical records. Use of protected health information (PHI) for the purposes of research is subject to the HIPAA Privacy Rule (Also known as “Standards for Privacy of Individually Identifiable Health Information”, Title 45 CFR, Part 160 and Subparts A and E of Part 164.)

Research involving retrospective review of existing data, documents, records and pathological or diagnostic specimens is permitted and may be eligible for expedited review or require full review (See Section F.1.) In both situations, the requirements for subject consent and Authorization for release of protected health information could be waived by the IRB, provided that the research met the requirements for such waivers as described in SECTION E.2.f. and g. These provisions apply only to retrospective use of existing records. If it is the intent of the investigator to obtain information prospectively, it is necessary for the investigator to obtain written consent and Authorization from the subjects to use their medical records and tissue specimens. Similarly, if the intent of the research changes from retrospective to prospective research, the investigator must re-apply to the IRB through expedited or full review to obtain approval to obtain written consent and Authorization from the subject to use the private information and tissue specimens.

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c. Confidentiality of Research data. To maintain confidentiality of research data, the investigator must protect information obtained from the subject to avoid unintentional access by others. Guidelines to investigators for developing procedures to address confidentiality include:

Use completely anonymized data whenever possible, including data where identifiers have not been collected, data where identifiers have been removed effectively, and data that have been aggregated (averages, ranges). Samples are not considered as anonymous if it is possible for any person to link the sample with its source, as might be the case with small samples, rare disease categories, specialized jobs, age, etc., even though the identifiers have been removed.

For identifiable data: limit the personal information recorded to that which is essential to the research; store personally identifiable data securely in a locked file or office and limit access to only investigators and authorized staff; code the data as early as possible and, if no longer necessary, dispose of the code linking the data to individual subjects when the data have been processed; strip the data of identifiers and provide only coded or anonymized data to other researchers; do not disclose personally identifiable data to anyone other than the research team without the written authorization of the subjects or their legal representative; spell out the conditions of confidentiality and risks of breach of privacy in the consent document to designate who and under what conditions the data, including identifiers, may be reviewed; and dispose of no-longer needed hard copy/computer based data containing identifiers in a manner designed to protect privacy (e.g., shredding, reformatting, etc.).

If the data and identifiers are considered to be sensitive, investigators may consider applying for or may be required to apply for a "Certificate of Confidentiality" when the disclosure of information learned about a subject could place the subject at legal risk and be particularly damaging (42 U.S.C. Section 241(d)). This Certificate protects against compulsory disclosure (such as a subpoena or court order) of research data that identifies a specific individual (not information in the aggregate), although review by federal agencies, such as FDA, is still permitted. Certificates are issued only "when the research is of a sensitive nature where the protection is judged necessary to achieve the research objectives." Various agencies within HHS provide these certificates.

The categories of research explicitly covered by the Certificate include:

- Research relating to sexual attitudes, preferences, or practices;
- Research relating to the use of alcohol, drugs, or other addictive products;
- Research pertaining to illegal conduct;
- Research involving the collection of information that if released could reasonably be damaging to the individual's financial standing, employability, or reputation;
- Research involving the collection of information that would normally be recorded in a patient's medical record which, if disclosed, could reasonably lead to social stigmatization or discrimination;

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- Research involving the collection of information pertaining to an individual's psychological well-being or mental health; and
- Genetic information.

In addition, Certificates may be issued for other categories of research considered sensitive because of specific cultural or other factors, upon justification. The Confidentiality Certificate does not govern the voluntary disclosure of identifying characteristics of research subjects, but only protects subjects from compelled disclosure of identifying characteristics. Researchers, therefore, are not prevented from the voluntary disclosure of matters such as child abuse or a subject's threatened violence to self or others. However, if a researcher intends to make such voluntary disclosures, the consent form should clearly indicate this.

In accordance to Network 2 Information Security Incident Reporting Policy 10N2-147-07: Employees should immediately report incidents involving theft, loss, or compromise of any VA Government Furnished Equipment (VAGFE) or non-VA Owned Equipment (OE) device used to transport, access or store VA information, or any VAPI to his/her supervisor and the local ISO.

In any research incident involving compromised personal information, written notification letters intended for distribution to the research subject(s) will obtain IRB approval prior to distribution.

7. Use and storage of tissue from research subjects.

It is also acceptable to use human biological specimens in research. Such specimens are defined as any material derived from human subjects, such as blood, urine, tissues, organs, hair, nail clippings or any other cells or fluid whether collected for research purposes or as residual specimens from diagnostic, therapeutic, or surgical procedures. With the publication of VHA Directive 2000-043 (Banking of Human Research Subjects' Specimens, dated 11/6/2000, and nationally released on 3/28/2001), all new proposals will comply with the guidance detailed in the Directive and all previously established projects will come into compliance at their next IRB review (e.g., continuing review date or date of review of a revision or amendment, if earlier).

If specimens are to be sent to a non-VA institution for testing/use as defined in the protocol and are destroyed once the specific analyses are performed, the remainder of the specimens must be destroyed or returned to the VA for destruction. If the specimens are destroyed at another institution, that institution must certify the destruction of the specimens in writing. Human biological specimens collected under a VA-approved protocol are not considered to be "banked" (stored) specimens if the specimens are used for only the specific purposes defined in the protocol and are destroyed either when the specific testing/use is completed or at the end of the protocol.

Specimens collected and stored for future research purposes are considered "banked" specimens. These specimens must be banked in a VA-sponsored or VA-approved tissue bank. Reuse of these specimens must be consistent with the consent under which they were collected, and the

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reuse must only occur through a VA-approved protocol. A VA-sponsored tissue bank is a tissue repository or storage facility at a VA facility or approved off-site location that operates in accordance with VA regulations. It contains human biological specimens collected under VA-approved research protocols that are under both VA ownership and VA control. In contrast, a VA-approved bank is an approved tissue bank located in a non-VA facility that has appropriate approval from the Chief Research and Development Officer (CRADO). It must also meet safeguards similar to those required for a VA-sponsored tissue bank. Non-VA sites that may not be acceptable include non-academic, for-profit institutions, such as pharmaceutical companies.

If the protocol requires that the specimens be analyzed/used at a non-VA institution, a written understanding between the VA investigator and the non-VA institution must specify the analysis/use as defined in the protocol. The agreement must also specify that any remaining quantities of the specimens shall either be destroyed or returned to the VA. If the remaining quantity is destroyed, that institution must certify the destruction of the specimens in writing. The remaining quantity may not be retained and/or stored by the non-VA institution.

The investigator storing the banked specimens must retain a copy of the original consent under which each specimen was collected, a record of the use of the specimens, and the protocols under which they are used.

In all uses of tissue, non-banked or banked, linking of the data generated by the specimens and the clinical data should occur within the VA and by VA investigators whenever possible. When this is not possible, the minimal amount of clinical data should be shared with those doing the statistical analyses. The clinical information that is shared should not contain any unique identifiers.

8. Studies Involving Investigational Devices. The Syracuse IRB does not currently review studies involving investigational devices.

9. Activities Preparatory to Research (45 CFR 164.512 (i)(1)(ii)). Data repositories (including VA medical records) may be used (i.e., accessed) by VA investigators for activities that are preparatory to VA research without the requirement to obtain either a HIPAA authorization from the subject or waiver of HIPAA authorization by an IRB or Privacy Board. This includes use of PHI for the preparation of a research protocol prior to submission to the IRB(s). "Preparatory to research" activity is the only instance of access for research purposes allowed in VHA without a written HIPAA authorization signed by the individual, a waiver of HIPAA authorization by an IRB or Privacy Board, or approval by the IRB(s). This access is granted only to VHA researchers. Non-VHA researchers may not access VHA data for reviews preparatory to research. Additionally, the following holds true:

a. Representations by the Investigator. The investigator must make the representations necessary for preparatory access as required by the HIPAA Privacy Rule and document it in the investigator's research files. The representations required by the HIPAA Privacy Rule

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are:

- (1) The access to PHI is only to prepare a protocol;
- (2) No PHI will be removed from the covered entity (i.e., VHA); and
- (3) The PHI accessed is necessary for preparation of the research proposed.

b. **Aggregate Data.** Only aggregate data may be recorded in the researcher's files, and these aggregate data may be used only for background information, to justify the research, or to show that there are adequate numbers of potential subjects to allow the investigator to meet enrollment targets or sample size requirements.

c. **No Recording of Individually Identifiable Health Information.** Individually identifiable health information may not be recorded.

d. **No Recruiting From Data.** Data or information reviewed may not be used for contacting or recruiting subjects.

e. **Repository Requirements.** Investigators must comply with all other access requirements set by the repository of interest.

f. **Agreements.** See VHA Handbook 1200.12 regarding requirements for Data Use Agreements (DUA) or Data Transfer Agreements (DTA).

***NOTE:** Pilot studies are full-fledged research studies that must be approved by the IRB, when human subjects are involved. Pilot studies are not considered to be "activities preparatory to research."*

***NOTE:** No formal IRB determination of exemption from human subject protection requirements is needed if all of the conditions listed above are satisfied.*

10. Research on Decedents' Information. PHI of a person who has passed away may be used or disclosed without consent or authorization if the investigator demonstrates to the holder of the records (e.g., the Syracuse VAMC through the IRB) all of the following:

- the use or disclosure sought is solely for research on the PHI of decedents;
- their deaths are documented to the satisfaction of the record holder; and
- the PHI for which use of disclosure is sought is necessary for the research purposes.

D. ELIGIBILITY FOR PERFORMING RESEARCH:

Clinical research studies may be conducted at the Syracuse VA Medical Center and its research affiliated VA facilities by VA personnel only. An individual not holding a paid appointment may conduct research only with the endorsement of a regular staff member who is willing to assume full responsibility as Principal Investigator for the ethical and scientific conduct of the project. As well, a non-VA investigator must apply for and be granted a Without Compensation (WOC)

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appointment. All principal investigators must have documented completion of all elements of IRB training prior to any contact with research study subjects.

Other VA or WOC employees may serve on research projects, as needed. However, principal investigators must list all individuals participating on the study, such as sub-investigators, clinical coordinators, research fellows, and residents. This list will be submitted to the Research Administration office and reviewed by the IRB with each new protocol application, on annual progress reports and subsequently as changes occur. All individuals listed must have documented completion of all HRPP educational requirements prior to any contact with research study subjects. *To be eligible to inform prospective subjects about aspects of a study and conduct the informed consent process, individuals must be a VA employee (paid or WOC), must have an approved scope of practice/responsibility, must be knowledgeable about the consenting process and the research to be conducted, must have completed all IRB educational and training requirements, must have all credentials verified; and must be included on the IRB approved list of individuals participating on the study. If someone other than the investigator obtains the consent, the investigator must formally delegate this responsibility and the person so designated must have received the appropriate training to perform this activity.*

For studies with greater than minimum risk, a qualified, trained, appropriately credentialed Co-PI or co-investigator (Co-I) must be appointed to direct the research during times when the PI is on leave or otherwise unavailable. This requirement is designed to enhance subject safety by having an investigator (PI or Co-PI/Co-I) available at all times to provide coverage for all subject-related aspects of the research including obtaining informed consent, evaluating subject eligibility, writing prescriptions, examining subjects, evaluating/managing/reporting SAEs, AEs, protocol deviations, etc.

E. REQUIREMENTS FOR SUBMISSION OF MATERIALS FOR REVIEW BY IRB:

Submission forms are located on the R&D website:

<http://www.visn2.va.gov/apps/visn2shared/research/syr/syrforms.cfm>

1. Requirements for Submission of New Protocols.

Application packets for research projects are available through the R&D website or by contacting the research office. All of the forms necessary for completing the application, including forms and guides for preparing the VA Research Informed Consent Document, Financial Conflict of Interest Form, IRB educational items, etc. can be located on the VA R&D website.

If the research project is being submitted for extra-mural funding from sources such as VA Merit Review, NIH, etc., additional required forms are available in the research office.

In instances where the investigator plans to conduct research at external sites that are engaged in the research (e.g., VA Investigators working on VA paid time at a non-VA institution), the IRB must be informed of:

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- Contact information for the site.
- Whether the site has granted permission for the research to be conducted.
- Whether the site has an IRB and if so, whether it has approved the research or will rely on the Syracuse VA IRB.

Once completed, the required materials must be submitted to the IRB Office by the first of the month for that month's next scheduled IRB meeting in order to have sufficient time for the application to be processed and sent to IRB members for review. Proposals submitted on the deadline date must be received in the IRB Office no later than 3:00 p.m.

The specific requirements for content may differ depending on the requirements of funding agencies. At minimum, the following information should be included in all proposals (see * below):

- An abstract of approximately 250 words,
- A relevant review of the literature,
- Proposed hypotheses,
- The subject sample with inclusion and exclusion criteria (see ** below),
- Methods, procedures, and the anticipated risks associated with participation,
- Data analysis plans, including methods for maintaining the confidentiality of subjects,
- Literature references.
- Plan for monitoring subject safety (see ***below)

*Proposals that qualify for expedited review or exemption from IRB review because of minimal or no risk and are only for local submission need not have a formal presentation of all of the elements listed. However, sufficient information must be presented to allow for judgment of merit, assessment of minimal or no risk and assurance of confidentiality of information relating to subjects. The Request to Review Research Proposal form must be completed for all human subject research proposals.

**Current Federal and VA regulations require that whenever possible and scientifically desirable, researchers should include women and minorities in their research, especially in population-based studies. If these populations are excluded or inadequately represented, the investigator must provide a compelling rationale for their exception. Attention must be paid to issues of research design and sample size related to the composition of the study population by gender and race/ethnic group.

***Monitoring Safety

a. Describing Data and Safety Monitoring Plan for Prospective Studies. This means the investigator describes the data and safety monitoring plan for prospective studies. This plan must

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include, but is not limited to, the following:

- (1) What safety information will be collected including SAEs (see VHA Handbook 1058.01);
- (2) How the safety information will be collected (e.g., with case report forms, at study visits, by telephone calls with subjects);
- (3) The frequency of data collection including when safety data collection starts;
- (4) The frequency or periodicity of review of cumulative safety data;
- (5) If not using a DMC, and if applicable, statistical tests for analyzing the safety data to determine if harm is occurring;
- (6) Provisions for the oversight of safety data (e.g., by a DMC); and
- (7) Conditions that trigger an immediate suspension of the research, if applicable.

***NOTE:** The data and safety monitoring plan may vary depending on the potential risks, complexity, and nature of the study. The use of an independent DMC needs to be considered if there are multiple clinical sites, the study is blinded, interventions are high-risk, vulnerable populations are included, or when required by the funding organization, FDA, sponsor, or other relevant entity.*

b. Describing Data and Safety Monitoring Plan for Retrospective Studies. This means the investigator describes the safety and monitoring plan for retrospective studies, including studies involving pre-existing data and biological specimens. When applicable, the plan needs to include, but is not limited to, the following:

- (1) A discussion with the subject of potential study outcomes that may have an effect on the subject's health or well-being; and
- (2) A procedure to determine when and how to notify individual subjects or their health care providers of findings that may affect the subjects' health.

c. Differentiating Usual Care from Research. This means the investigator provides for usual care. If the protocol involves "usual care," the protocol must either include a narrative section or there must be a separate document in the IRB application that clearly differentiates the research intervention(s) from "usual care" (whether the "usual care" is limited to one "arm" of the study or is being delivered to all study subjects) (See subpar 9j(4)).

(1) When a study involves "usual care," in the protocol or a separate document in the IRB application the investigator must clearly designate the individual or entity (e.g., the appropriate research personnel versus the subject's health care provider) responsible for relevant aspects of both the research and the usual care.

(2) The subject needs to be able to identify which activity (e.g., treatment or service) is research, and which is usual care, and know who (the researcher or the subject's health care provider) is responsible for:

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- (a) Explaining potential risks and benefits of the treatment or service to the subject;
- (b) Providing the treatment or service;
- (c) Monitoring the treatment or service, as applicable;
- (d) Defining whether the adverse events result from usual care or research, as applicable;
- (e) Alerting the subject if there is a problem with the treatment or service (e.g., a newly discovered risk, a product recall); and
- (f) Documenting the subject's clinical course while receiving the treatment or service, as applicable.

NOTE: *The researcher and the subject's health care provider may be the same individual. If they are different individuals, and the subject's health care provider is not involved in the research study, the health care provider is not considered to be a member of the research team.*

2. Required IRB Submittal Forms. The requirements for administrative information differ depending on the type of research project being proposed. The following forms need to be completed or information submitted, when appropriate:

- (a) Request to Review Research Proposal Application (*completed and signed by all parties (PI, Co-PI, Sub Investigators & Careline Leader)*)
- (b) Study Abstract (brief synopsis of study in lay terms)
- (c) HIPAA Authorization and Revocation forms and/or HIPAA Waiver Request Form
- (d) Consent Document (*or request to waiver/alter informed consent as appropriate*)
- (e) Study Protocol (3 copies)
- (f) Subject Questionnaires, Advertisements, Recruitment Materials (pamphlets, posters, letters)
- (g) Copies of all protocol data collections tools, Case Report Forms (CRFs), etc.
- (h) Investigator's Brochure (3 copies)
- (i) Completed Data Security Form
- (j) Letters/Memos of Support: (Sample Pharmacy Support Memo available on website)
- (k) Lab Service Support Memo (if necessary)
- (l) Support Memo from any other Syracuse/Canandaigua/Bath VAMC service/section (if necessary)
- (m) Sponsor Contract through CNYRC (or other arrangements for financial coverage of Pharmacy costs, IRB review fee, lab service, etc.)
- (n) VA Form 10-9012 Investigational Drug Information Record (*if necessary*) *Investigational Drug Information Record, is required for only those drugs that are not currently found in the AHFS Drug Information book. These include all drugs which have been released by the FDA for investigational use, an approved drug put to a new use, non-standard dosages levels or routes of administration and those which have been given IND Numbers (Investigational New Drug Application Numbers) by the FDA.*
- (o) FDA Form 1572 (Statement of Investigator, *if necessary*)
- (p) Investigator Data Sheet (*VA form 10-5368 if PI has not been involved in research as a PI in the past 12 months*)

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- (q) CV (*PI and each research staff member*).
- (r) Investigator's Conflict of Interest Form
- (s) Syracuse VAMC Addendum to Clinical Functional Statement: all Syracuse VAMC principal investigators are required to have an addendum in their Clinical Functional Statements identifying research duties/activities.
- (t) Scope of Work Memos from collaborators/coordinators/staff (Submit one form from each: PI, Sub-I, NP, all Coordinators and other staff involved with the conduct of the study). PIs may use the Syracuse VAMC Addendum to Clinical Functional Statement in lieu of the Scope of work, which documents their Clinical Research role and responsibilities.

3. INFORMED CONSENT

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

a. Circumstances Under Which Informed Consent May Be Sought. The Common Rule requires (38 CFR 16.116):

- (1) The investigator to seek informed consent only under circumstances that:
 - (a) Provide the prospective subject or the subject's LAR sufficient opportunity to read the informed consent document when applicable,
 - (b) Provide the prospective subject, or the subject's LAR, sufficient opportunity to consider whether or not to participate, and
 - (c) Minimize the possibility of coercion or undue influence.
 - (d) Consent for research must be obtained from each research subject before taking photographs or making voice or video recordings that will be used for research purposes.
 - i. Unless the IRB grants a waiver of documentation of the consent process for research, the consent document for research must include a discussion of why photographs, or voice or video recordings are being taken for the research, who will have access to them, and what their disposition will be after the research is completed.
 - ii. When the research subject is a patient (either an inpatient or outpatient), the subject must sign VA Form 10-3203 to permit photographs or video and voice recordings that will be used for research purposes even if the IRB has waived the requirement for documentation of consent for research. Photography or recordings cannot occur prior to the

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patient's granting such permission.

iii. When the research subject is a patient, the subject's signed and dated VA Form 10-3203 must be placed into the medical record along with, if applicable, the signed and dated research consent document (i.e., VA Form 10-1086). The signed VA Form 10-3203 must be obtained and placed in the subject's medical record, even if the IRB has waived documentation of consent for research.

(2) The information that is given to the subject or the subject's LAR must be in language understandable to the subject or the subject's LAR.

(3) No informed consent, whether oral or written, may include any exculpatory language through which the subject or the subject's LAR:

- (a) Is made to waive, or appear to waive, any of the subject's legal rights; or
- (b) Releases, or appears to release, the investigator, the sponsor, the institution, or its agents from liability for negligence

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

c. Observing the Process. The IRB has the authority to observe or have a third party observe the informed consent process. It has the authority to review patient records to make sure that the necessary documents, as required, are placed in the patient's records, that the patient is indeed eligible for such study, and any other details of the research that may be deemed pertinent. Any procedural or protocol violations which are found will be brought to the attention of the Chair IRB, the ACOS for R&D, the investigator, appropriate institutional officials, and to the IRB.

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

(1) All required elements must be completed as well as any additional elements required by the IRB which may include, but not be limited to those in Section f of this policy.

(2) The informed consent form must contain a designated block for each required signature (e.g., subject, person obtaining the informed consent, and witness when applicable) and for the date of each signature.

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e. REQUIRED ELEMENTS OF INFORMED CONSENT

a. Elements of Informed Consent Required by the Common Rule. Except as provided in Paragraphs 34, 35 and 36 of Handbook 1200.05, 38 CFR 16.116(a) requires the following elements of informed consent be provided to each subject:

(1) **A Statement That the Study Involves Research.**

(2) **An Explanation of the Purposes of the Research.**

(3) **The Expected Duration of the Subject's Participation.** A description of the expected length of the subject's commitment to active participation in the interventions or interactions of the study, including long-term follow-up. This does not include the time after all interventions and interactions with the subject have ended and the study activities include only analysis of specimens and/or data, and/or preparations for publication of results.

(4) **A Description of the Procedures to be Followed.**

(5) **Experimental Procedures.** Identification of any procedures that are experimental (38 CFR 16.116(a)(1)).

(6) **Risks or Discomforts.** A description of any reasonably foreseeable risks or discomforts to the subject (38 CFR 16.116(a)(2)).

(a) This description is to include, but not be limited to, physical, social, legal, economic, and psychological risks.

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

(7) **Benefits.** A description of any benefits to the subject or to others that may reasonably be expected from the research (38 CFR 16.116(a)(3)).

(8) **Alternatives.** A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject (38 CFR 16.116(a)(4)).

(9) **Confidentiality.** A statement describing the extent to which confidentiality of records identifying the subject will be maintained (38 CFR 16.116(a)(5)). If appropriate, a statement that Federal agencies including, but not limited to, the FDA, OHRP, ORO, and the VA Office of the Inspector General (OIG) may have access to the records. If an FDA-regulated test article is involved, FDA requires a statement that the FDA may choose to inspect research records that include the subject's individual medical records.

(10) **Research-Related Injury**

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

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

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

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

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

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

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

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

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

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

f. ADDITIONAL ELEMENTS OF INFORMED CONSENT

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

g. DOCUMENTATION OF INFORMED CONSENT

Informed consent must be documented prospectively by the use of a written consent form approved by the IRB (38 CFR 16.117(a), unless documentation of informed consent has been explicitly waived by the IRB (38 CFR 16.117(c)). **NOTE:** *Email communications do not constitute documentation of informed consent.*

a. Consent Form. VA Form 10-1086, Research Consent Form, must be used as the consent form for VA research. The only exception is that a DoD informed consent form may be employed for active duty military personnel participating in VA research at DoD sites when VA-specific language is not necessary (e.g., when language for treatment of research related-injury is not needed because active duty military personnel are covered by DoD). The informed consent form must be the most recent IRB-approved informed consent form that includes all the required elements and, as appropriate, additional elements.

(1) The requirement to utilize VA Form 10-1086 to document informed consent applies to all VA-approved research including, but not limited to, studies in which VA investigators working on VA Research enroll subjects at an affiliate hospital or other sites outside VA (e.g., community centers or shopping malls).

(2) The “most recent” IRB-approved version of the informed consent form contains the date of the version of the informed consent form most recently approved by the IRB (e.g., in a header or footer). For instance, if the most recent version of the informed consent sent for approval by the IRB was the June 14, 2009, version, and the IRB approved it on July 1, 2009, the investigator must ensure the informed consent form contains the date June 14, 2009, on each page. The June 14, 2009, version would continue to be the most recent version even after approved by the IRB during the continuing review process (i.e., if there is no change in the informed consent form at the time of continuing review, it is not considered a new version).

b. IRB Approval Date. The IRB approval must be documented in the IRB minutes or IRB protocol files for those studies reviewed by the expedited process. IRB correspondence with the investigator must clearly indicate which version of the informed consent form has been approved. The IRB approval date must be documented by the use of a stamp or preprinted box on each page of the informed consent form. This stamp or preprinted box must indicate the most recent date of IRB approval of the informed consent form. The IRB must maintain a

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copy of the approved informed consent form in its records.

c. Signatures and Dates. The informed consent form must be signed and dated by:

- (1) The subject or the subject's LAR (38 CFR 16.117(a)),
- (2) The person obtaining the informed consent, and
- (3) A **witness is not required** to sign an informed consent form (**Unless** the IRB requires a witness signature) A witness, if required by IRB (e.g., the IRB may require a witness if the study involves an invasive intervention or an investigational drug).

(a) The witness is required to witness only the subject's or subject's LAR's signature, not the informed consent process (e.g., if the subject does not want the witness to know the nature of the research study), unless the sponsor or IRB requires the witness to witness the informed consent process.

(b) The witness cannot be the person who obtained informed consent from the subject, but may be another member of the study team or may be a family member.

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

e. Copies of Signed Consent Form

- (1) A copy of the signed and dated informed consent form must be provided to the subject or the subject's LAR (38 CFR 16.117(a)).
- (2) Where applicable, a copy of the signed and dated informed consent form must be placed in the medical record in accordance with VHA Handbook 1907.01.
- (3) A Copy must be submitted to the IRB Office.

f. Written Informed Consent With All Required Elements. Except as provided in section h (below). The consent may be in the form of a written consent document that embodies the elements of informed consent required by 38 CFR 16.116. This form may be read to the subject or the subject's LAR, but in any event, the investigator must give either the subject or the representative adequate opportunity to read it before it is signed (38 CFR 16.117(b)(1));

h. WAIVER OF DOCUMENTATION OF INFORMED CONSENT

a. **Criteria for Waiver.** The IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds and documents either (38 CFR 16.117(c)):

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(1) **Waiver of Documentation of the Consent Process - Based on Harm:** 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 and the research is not FDA regulated (38 CFR 16.117(c)(1)); or

(2) **Waiver of Documentation of the Consent Process - Minimal Risk:** That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context (38 CFR 16.117(c)(2)).

b. **Written Statement.** In cases in which the documentation requirement is waived, IRB may require the investigator to provide subjects with a written statement regarding the research. The IRB will review the written description of the information that will be provided to subjects prior to granting approval for the waiver of documentation of informed consent. (38 CFR 16.117(c)(2)).

c. **IRB Documentation.** IRB must document its determinations regarding a waiver of documentation of informed consent in the IRB minutes or in the protocol file.

d. **Informed Consent Process.** Unless IRB has granted a waiver of informed consent (see section i below), even if IRB has granted a waiver of documentation of informed consent, the investigator, or designee, must still perform an adequate informed consent process.

i. WAIVER OF INFORMED CONSENT

a. **Government Research and Informed Consent is Not Practicable.** The IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent; or waive the requirement to obtain informed consent, provided the IRB finds and documents that (38 CFR 16.116(c)):

(1) The research is to be conducted by, or is subject to, the approval of state or local government officials and is designed to study, evaluate, or otherwise examine (38 CFR 16.116(c)(1)):

- (a) Public benefit of service programs;
- (b) Procedures for obtaining benefits or services under those programs;
- (c) Possible changes in or alternatives to those programs or procedures; or
- (d) Possible changes in methods or levels of payment for benefits or services under those programs.

(2) The research could not practicably be carried out without the waiver or alteration (38 CFR 16.116(c)(2)).

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b. When following FDA regulations, the IRB is prohibited from waiving or altering the consent process.

c. **Minimal Risk Research.** The IRB may approve a consent procedure that does not include, or that alters, some or all of the elements of informed consent; or the IRB may waive the requirements to obtain informed consent, provided the IRB finds and documents that (38 CFR 16.116(d)):

- (1) The research involves no more than minimal risk to the subjects (38 CFR 16.116(d)(1));
- (2) The waiver or alteration will not adversely affect the rights and welfare of the subjects (38 CFR 16.116(d)(2));
- (3) The research could not practicably be carried out without the waiver or alteration (38 CFR 16.116(d)(3)); and
- (4) Whenever appropriate, the subjects are provided with additional pertinent information after participation (38 CFR 16.116(d)(4)).

d. **Other Applicable Federal, State, or Local Laws.** The informed consent requirements in this Handbook are not intended to preempt any applicable Federal, state, or local laws which require additional information to be disclosed in order for informed consent to be legally effective (38 CFR 16.116(e)).

e. **IRB Documentation.** The IRB must document its determinations regarding a waiver of informed consent in the IRB minutes or in the protocol file.

j. SURROGATE CONSENT

Under appropriate conditions, investigators may obtain consent from the LAR of a subject (i.e., surrogate consent).

a. **Assessment of Capacity.** Before persons who lack decision-making capacity may be considered for participation in any VA research, the IRB must find that the proposed research meets all of the conditions contained in R&D SOP 151-06

b. **Investigators' Responsibilities for Surrogate Consent.** Investigators must:

- (1) Provide the IRB with a description of the procedures to ensure that subjects' LARs are well informed regarding their roles and obligations to protect persons who lack decision-making capacity.
- (2) Provide information (i.e., informed consent process and HIPAA authorization) to the subjects' LARs that would ordinarily be required by this policy to be made to the subjects themselves if they had decision-making capacity.

c. **LARs**

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(1) **Authorized Person.** The following persons are authorized to consent on behalf of persons who lack decision-making capacity in the following order of priority (38 CFR 17.32(e)) (see subpar. 3aaa for personal representative for the purposes of signing a HIPAA authorization):

- (a) Health care agent (i.e., an individual named by the individual in a Durable Power of Attorney for Health Care (38 CFR.17.32(a)(iii));
- (b) Legal guardian or special guardian;
- (c) Next of kin in this order: a close relative of the patient 18 years of age or older, in the following priority: spouse, child, parent, sibling, grandparent, or grandchild; or
- (d) Close friend.

***NOTE:** An individual who is qualified as an LAR to provide informed consent on behalf of a prospective research subject may not always qualify as a personal representative for purposes of consent to use or disclose a human subject's PHI (i.e., signing a HIPAA authorization). Therefore, in circumstances involving authorization for use or disclosure of a human subject's PHI, the investigator must ensure the LAR meets the requirements of a personal representative (legal guardian or power of attorney) in HIPAA and the Privacy Act of 1974 prior to the LAR's signing a HIPAA authorization (see VHA Handbook 1605.1).*

(2) **Responsibilities of LARs.** LARs are acting on behalf of the potential subjects, therefore:

- (a) LARs must be told that their obligation is to try to determine what the subjects would do if able to make an informed decision.
- (b) If potential subjects' wishes cannot be determined, the LARs must be told they are responsible for determining what is in the subjects' best interests.
- (c) LARs generally assume the same rights and responsibilities as the individuals who lack decision-making capacity in the informed consent process (see 38 CFR 17.32(e)).

d. **Dissent or Assent.** If feasible, the investigator must explain the proposed research to the prospective research subject even when the surrogate gives consent. Although unable to provide informed consent, some persons may resist participating (i.e., dissent to participate) in a research protocol approved by their representatives. Under no circumstances may a subject be forced or coerced to participate in a research study even if the LAR has provided consent.

e. **Fluctuating Capacity.** Investigators, IRB members, and LARs must be aware that decision-making capacity may fluctuate in some subjects. For subjects with fluctuating decision-making capacity or those with decreasing capacity to give consent, a re-consenting process with surrogate consent may be necessary.

k. HIPAA AUTHORIZATION

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a. **Written Authorization.** A written HIPAA authorization signed by the individual to whom the information or record pertains is required when VA health care facilities need to utilize individually-identifiable health information for a purpose other than treatment, payment, or health care operations (e.g., research) (VHA Handbook 1605.1).

(1) In accordance with 45 CFR 164.508(b)(3)(ii), an authorization for a use or disclosure of psychotherapy notes may not be combined with any other authorization for a use or disclosure unless the other authorization is also for a use or disclosure of psychotherapy notes.

(2) The HIPAA authorization for the use or disclosure of individually-identifiable health information for a VA research study must be a standalone document (i.e., not combined with any other type of written permission for the same research study, including the research informed consent form).

(3) An IRB does not have the authority to approve a HIPAA authorization unless it is incorporated into the informed consent document. Since this Handbook requires the HIPAA authorization and the informed consent form to be separate documents, the IRB cannot approve a HIPAA authorization for a VA research study. However, the IRB may waive the requirement for a HIPAA authorization.

(4) The IRB must ensure the protocol and informed consent form are consistent with the HIPAA authorization.

NOTE: *Research involving limited data sets may be performed in accordance with VHA Handbook 1605.1. A limited data set may not be de-identified information or data. VHA may disclose a limited data set for research pursuant to a data use agreement.*

b. **Waiver of HIPAA Authorization (see 45 CFR 164.512(i)(2)).** A request from an investigator for the IRB to waive the HIPAA authorization must be accompanied by sufficient information to allow the IRB to make the required determination. The IRB must document its findings and this documentation must include, but is not limited to, all of the following:

- (1) Identification of the IRB of record.
- (2) Date of IRB approval of waiver of HIPAA authorization.
- (3) Statement that the waiver of HIPAA authorization satisfies the following criteria:

(a) The use or disclosure of the requested information involves no more than minimal risk to the privacy of individuals based on, at least, the presence of the following elements:

1. An adequate plan to protect the identifiers from improper use and disclosure;
2. An adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise mandated by applicable VA or other Federal requirements; and
3. Adequate written assurances that the requested information will not be reused or

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disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the requested information would be permitted by the Privacy Rule.

- (b) The research could not practicably be conducted without the waiver; and
 - (c) The research could not practicably be conducted without access to and use of the requested information.
- (4) A brief description of the PHI for which the IRB has determined use or disclosure to be necessary.
- (5) The specific findings on which the IRB based its decision to grant the waiver of HIPAA authorization.
- (6) Identification of the IRB review procedure used to approve the waiver of HIPAA authorization (either convened IRB review procedures (38 CFR 16.108(b) or expedited review procedures (38 CFR 16.110).
- (7) Signature of Chair of the IRB, or qualified voting member of the IRB designated by the Chair, on the HIPAA authorization waiver document.

***NOTE:** The documentation of the IRB's findings may be in the IRB minutes or the IRB protocol file. If IRB does not document the waiver of authorization as required, the waiver is not valid.*

l. Master List of Subjects: The PI will maintain a master list of subjects after informed consent has been obtained, unless this requirement has been waived by the IRB (VHA Handbook 1200.05 Subparagraph 9u).

- a. The IRB may waive the requirement for the investigator to maintain a master list for a given study if both of the following conditions are met:
 - (1) There is a waiver of documentation of the consent process, and
 - (2) The IRB determines that including the subjects on such a master list poses a risk to the subjects from a breach of confidentiality.

If IRB waives the requirement to maintain such a master list, IRB must provide written documentation in the IRB minutes or IRB protocol file justifying the waiver.

m. Data Security Checklist Form: All projects require the PI to complete the Data Security Checklist for Principal Investigators and Assessment of security of VA research data shared outside the VA. The Information Security Officer (ISO) will be provided with a copy of the research protocol along with the certification documents in order to review and approve the data security and privacy assessments. These will be reviewed prior to IRB review. The ISO will inform the IRB of any items of note in regards to the data assessments provided.

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n. Cost and Impact Statements. Locally created forms must be filled out to determine the impact of and patient costs associated with the proposed research project. Specifically, if drugs are to be administered, a Pharmacy Protocol Participation Agreement memo must be filled out and sent with a copy of the study protocol and investigator's brochure (if available) to the Research Pharmacist (mail code 119), ext. 52495. Once the Pharmacy Protocol Participation is agreed to and signed off by the Pharmacy Chief, it must be forwarded with the completed application to IRB Office. In addition, if requested, a Patient Treatment Cost Impact statement must be completed to estimate the costs per VA study patient and/or total costs that will be incurred over and above the costs involved in standard treatment. If submitted, a review of the impact statement will be discussed at the time that the project is reviewed by the IRB.

o. Disclosure of Conflict of Interests of Clinical Investigators. This form must be completed and signed by all staff involved on the study. This form is required for all submitted proposals to the IRB.

p. Copies of Contracts. If the proposed research protocol is being funded in whole or in part by a third party (e.g., a pharmaceutical company), a copy of the AAHRPP Sponsored Research Contract Requirements New Contract Checklist, a copy of the contract, duly executed by the third party entity and the organization administering the funds (e.g., Central New York Research Corporation, SUNY UMU) must be submitted to the IRB Office. Review of the contract further allows the IRB to evaluate any potential conflicts of interest to which the investigator and/or institution may be subject.

4. Requirements for Continuing Review Progress Reports.

In compliance with federal regulations, the IRB will "...conduct continuing review...at intervals appropriate to the degree of risk, but not less than once per year..." In accordance with regulations, the IRB interprets "not less than one year" review to mean "review on or before the 1-year anniversary date of the previous IRB approval...even though the research activity may not begin until some time after the IRB has given approval." The IRB Office will also supply the primary reviewer(s) with a copy of the project's MIRB protocol history for review purposes.

a. Report Requirements for Continuing Review. The continuing review progress report is an internal document to be filled out and submitted by each principal investigator. The report is designed to obtain information concerning progress since the last reporting period on the project, the number of subjects studied, protocol modifications, adverse events, subject withdrawals, unanticipated risks to participants or others, complaints, updated Investigator's Brochure, and any recent literature, interim findings, relevant multi-center trial reports or other relevant information, especially information about risks associated with the research. *To consider whether recruitment methods, enrollment procedures and selection criteria fairly distribute the burdens, risks and benefits of the research, the number of subjects enrolled must be further broken down by gender, minority status and, if applicable, number of potentially vulnerable subjects enrolled into the study.* In addition, the investigator must submit a copy of the latest

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version of the consent document used in that study. This is required as a quality control measure to assure that the investigator is indeed using only the approved (and most recent version, if amended) form of that document. The investigator must submit a master list of names and social security numbers of patients enrolled in the project since study onset, using the IRB Office-generated form. The PI must also ensure that they have submitted a copy of the signed, completed consent document and Authorization Form from each subject enrolled onto the study during the past year. The PI must submit a list of all study personnel working on that particular human study protocol. This list will be reviewed by the Research Office to insure all study personnel have completed mandatory HRPP education requirements. Finally, the PI must determine if there have been any changes in the last year of approval for the PI or any of the sub-investigators listed on this protocol in regards to conflict of interest, which may include financial or commercial interest in the study being conducted. This may also include supervisory relationships, administrative or financial agreements between the sponsor and investigator(s) and/or family members of the investigator(s) such as monetary payments and/or stock holdings. Disclosure of Conflict of Interest for Clinical Investigators must be revised and signed by the PI and any study staff involved on the study if it is determined there have been changes.

b. Penalties for Failure to Submit Continuing Review Progress Report on Time.

When continuing review occurs annually and the IRB performs continuing review within 30 days before the IRB approval period expires, the IRB may retain the anniversary date as the date by which the continuing review must occur. There is no provision for any grace period to extend the conduct of research beyond the expiration date of IRB approval. If approval expires:

- (1) The IRB office will promptly notify the investigator.
- (2) The investigator must:
 - (a) Stop all research activities including, but not limited to, enrollment of new subjects; continuation of research interventions or interactions with currently participating subjects; and data analysis.
 - (b) Immediately submit to the IRB Chair a list of research subjects who could be harmed by stopping study procedures.
 - (3) The IRB Chair, with appropriate consultation with the Chief of Staff, determines if subjects on the list may continue participating in the research interventions or interactions.
 - (4) Once the study approval has expired, IRB re-review and re-approval must occur before the study can resume. The IRB cannot retrospectively grant approval to cover a period of lapsed IRB approval.

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c. Procedures for Notification of Report Dates: While it is the responsibility of the principal investigator to submit the required continuing review progress report in a timely manner for review, the IRB Office will use a data base "early warning" system to keep track of the status of all ongoing IRB approved projects and will send a reminder memo to the investigator at one, two and three months before the due date of the progress report (e-mail messages or telephone calls can also be utilized for the reminders). These notices will remind PIs of the review requirement, date when the project and consent document will expire if not reviewed, and the penalty for not filing in a timely manner. If there has been no response, then a final memo, telephone call or e-mail message will be sent directly to the investigator as final reminder of the deadline and consequences. If the report is not filed by the deadline, the IRB will set into motion the penalties noted above.

4. Requirements for Submission of Modifications and Amendments to Protocols. All amendments to the study or changes in the informed consent form must be reviewed and approved in writing by the IRB prior to the investigator's initiating the changes, except when necessary to eliminate immediate hazard(s) to the subject(s).
(See SOP 151-20)

5. Requirements for Reporting of Adverse Events.

a. **SAE Reporting.** The investigator must report all unanticipated internal or local SAEs, whether related or unrelated to the research, to the IRB as specified under R&D SOP 151-17 and VHA Handbook 1058.01.

b. **IRB Responsibilities for SAEs.** A qualified IRB voting member reviewer (or alternatively, the convened IRB) must review the reports of internal or local SAEs, and must determine and document whether the event is serious, whether it is anticipated or unanticipated, and whether it is related, possibly related, or probably related to the research in accordance with VHA Handbook 1058.01.

(1) **Documentation of Whether or Not Action is Warranted.** After taking into account considerations including, but not limited to, whether or not the study still meets IRB approval criteria under 38 CFR 16.111 and 38 CFR 16.116 (such as whether or not the risks to subjects have changed; whether or not the risk to benefit ratio has changed; and whether or not this constitutes new information that needs to be given to the subjects), the qualified IRB voting member-reviewer (or the convened IRB) must document whether or not one of the following applies in accordance with VHA Handbook 1058.01:

(a) Immediate Action Warranted. Immediate action (e.g., suspension of activities; notification of subjects) is necessary to prevent an immediate hazard to subjects in accordance with VA regulations at 38 CFR 16.103(b)(4)(iii), and review by the convened IRB is needed; or

(b) No Immediate Action Warranted. Review by the convened IRB is needed, but immediate action to prevent an immediate hazard to subjects is not warranted.

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(2) **Reporting to Convened IRB.** If the preceding determinations are made by a qualified IRB voting member reviewer, the determinations must be reported to the IRB at the IRB's next convened meeting in accordance with VHA Handbook 1058.01.

(3) **Reporting to the Facility Director.** If the qualified IRB voting member reviewer (or the convened IRB) determines that the AE is serious, unanticipated, and related, or possibly related, to the research, the IRB Chairperson must report the event to the VA facility Director as soon as possible, but no later than 5 business days after the determination (VHA Handbook 1058.01). The VA facility Director then has an additional 5 business days to report the event to ORO (VHA Handbook 1058.01).

(4) **Informed Consent Modifications.** If it is determined that an informed consent modification is warranted, the convened IRB must determine and document in its records whether or not previously enrolled subjects must be notified of the modification and, if so,

- (a) When such notification must take place, and
- (b) How such notification must be documented (see VHA Handbook 1058.01).

c. **Adverse Events of Research-Related Clinical Care.** When subjects experience adverse events while undergoing clinical care that is part of a research study, the clinical care adverse events must be disclosed to subjects in accordance with current VHA policy.

6. Requirements for Submission of Other Communications Including Audits, Monitoring Site Visits, Sponsor Queries.

(a) The investigator must notify the IRB Office of any monitoring site visits or audits conducted by the study's sponsor or sponsor's representative. This notification must include the date(s), time, location and copies of communications with the sponsor/representative. The investigator has the responsibility to notify the IRB Office as soon as the visit is scheduled, in order to allow the IRB Office adequate time for either the IRB Chair or the IRB Administrator to attend the entrance and exit interviews with the site visitor(s). It is also the investigator's responsibility to submit copies of any communications, such as audit results, monitoring queries, etc. that are exchanged with the study sponsor/monitor.

(b) **Research Compliance Officer (RCO) Audits:** The RCO is an individual whose responsibility is auditing and reviewing research projects relative to requirements for the protection of human subjects. The RCO conducts annual consent document audits and triennial regulatory audits on all research protocols. The IRB may require more frequent audits by the RCO or other means than those required in VHA policy (see VHA Handbook 1058.01). The IRB also may require the RCO to conduct more focused audits of one or more aspects of the study. The requirement to increase the frequency of audits or to audit specific aspects of the study may be based on considerations including, but not limited to:

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- Involvement of vulnerable populations;
- Level of risk;
- Phase I or Phase II studies;
- Involvement of FDA approved drugs for which there has been a new safety warning issued, or change in the labeling that indicates increased risks;
- Issues of noncompliance; or
- Data confidentiality or security concerns.

It is noted that the IRB is required to conduct audits which must include, but are not limited to:

- Criteria that might prompt increasing the frequency of audits beyond the minimal required frequency.
- The timeframe for reporting audit findings to the IRB.
- Types of corrective actions the IRB can require based on the audit findings.
- Who should implement and review the corrective actions.
- How to evaluate the results of any corrective actions.

The IRB accepts audits conducted by the research compliance officer to fulfill these auditing requirements.

F. THE REVIEW PROCESS

1. Types of Review.

Submitted protocols may qualify for an EXEMPTION from IRB review, be eligible for EXPEDITED REVIEW or require FULL FORMAL REVIEW. The determination of type of review cannot be made by the Investigator, but is initially made by the Chairman of the IRB after consultation, when appropriate, with the ACOS/R&D, other IRB members, and/or Ad Hoc reviewers. In accordance with regulations, this determination is based upon type of study, level of physical risks, and level of potential social, legal, financial, and psychological risks related to subject privacy and confidentiality.

a. Exempt Category (See SOP 151-08)

b. Expedited Category

Under federal regulations, certain types of research may be eligible for expedited review. The IRB may use an expedited procedure to review research (e.g. research protocols, including protocol-related materials, amendments, revisions, and continuing reviews) that involves no more than minimal risk to the subjects and in which the only involvement of human subjects is in one or more of specifically noted categories. Expedited reviews will be conducted by the IRB Chairperson or by one or more of the IRB members designated by the Chairperson with sufficient

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experience (IRB Related, Human Subject Research Related or based on their professional expertise) to conduct the review.

A review sheet (VA Form 10-1223) will be completed for all expedited reviews and will contain comments about the project and the consent form, a citation or description designating why it would fit within the regulations for expedited review, and the reviewer's recommendation for approval. For new protocols and revisions the reviewer's sheet will also contain a summary description of the proposed project and/or changes. The IRB Chairperson or designee conducting the expedited review may exercise all of the authorities of the IRB except that they may not disapprove the research. They will refer any research protocol that they would have disapproved to the full IRB for review. The Chairperson or designee may also refer other research protocols to the full IRB when they believe that full IRB review is warranted.

Upon approval by the IRB Chairperson or his designee, the principal investigator will be sent a letter of approval, indicating that the "expedited" procedure was utilized. The protocol may be approved for up to one year and must be subjected to the review process for continuing protocols. Protocols will be terminated on the advice of the principal investigator or administratively terminated after the approval period unless renewed and approved through the IRB continuing review procedures.

When the expedited review procedure is used, the IRB Chairperson or designee conducting the review will place these research protocols on the agenda of the next IRB meeting and note that they have been approved under this procedure. At the convened IRB meeting, any member may request that any activity that has been approved under the expedited procedure be reviewed by the IRB in accordance with non-expedited procedures. Under these circumstances, a formal motion will be noted in the minutes suspending all activity on the protocol pending further review by the full IRB. Similarly, the full R & D Committee may request that any activity that has been approved under the expedited procedure be reviewed by the IRB in accordance with non-expedited procedures. Under these circumstances, a formal motion will be noted in the R&D Committee minutes suspending all activity on the protocol pending further review by the full IRB. In either case, the principal investigators will be informed immediately after the meeting to halt all activity on the project pending further review by the full IRB.

Research that involves no more than minimal risk and involves only procedures listed in the following categories are appropriate for expedited review:

- 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.)

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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 nondisfiguring 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. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies 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 subject's 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;

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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 HHS 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 HHS 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 IRB as follows:

a) Where:

- (1) the research is permanently closed to the enrollment of new subjects;
- (2) all subjects have completed all research-related interventions; and
- (3) 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 IRB 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 categories in this list apply regardless of the age of subjects, except as noted. Children are defined in the HHS regulations as “persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted.” 45 CFR 46.402(a).

The expedited review procedure will 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.

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The IRB chair or his/her designee may use the expedited review procedure to review minor modifications to research protocols and informed consent documents in previously approved research during the period for which approval is authorized. A minor modification is defined as a change that would not materially affect an assessment of the risks and benefits of the study or does not substantially change the specific aims or design of the study. Examples of minor modifications may include:

- the addition of research activities eligible for Exempt or Expedited Review
- an increase or decrease in proposed subject enrollment supported by a statistical justification
- narrowing the range of inclusion criteria
- broadening the range of exclusion criteria
- alterations in the dosage form (e.g., tablet to capsule or oral liquid) of an administered drug, provided the dose and route of administration remain constant
- decreasing the number or volume of biological sample collections, provided that such a change does not affect the collection of data related to patient safety evaluations
- an increase in the length of hospitalization or number of study visits for the purpose of increased patient safety
- a decrease in the length of hospitalization or number of study visits, provided that such a decrease does not affect the collections of information related to patient safety evaluations
- alterations in human research subject payment or liberalization of payment with proper justification
- changes to improve the clarity of statements or to correct typographical errors, provided that such changes do not alter the content or intent of the statement
- the addition or deletion of qualified investigators
- the addition or deletion of study sites
- minor changes specifically requested by the IRB, or other duly constituted Research and Development Service committees/subcommittees.

c. Full Review Category

The IRB Office assigns one or more primary reviewers, consistent with protocol content and reviewers' expertise for each new project, continuing review progress report and proposed protocol change and then sets up the agenda for the meeting, and mails out the agenda items 1-2 weeks before each meeting. Adverse reaction reports are reviewed by the IRB as a whole with the representative from Pharmacy Service serving as the primary reviewer.

The primary reviewer(s) will receive all available protocol information, including master protocols, Investigator's brochures, all available correspondence to the investigator concerning the protocol, the local protocol application and a copy of the proposed consent document when the agenda is sent at minimal 1 week before the time of the next meeting. The other members of the IRB will receive copies of the local protocol (if applicable), the abstract, the Request to

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Review Research Form, the proposed consent document, the covering letter, and additional details which may be necessary to allow evaluation of the explanations provided by the consent document.

Each primary reviewer and ad hoc reviewer of new projects will be provided with a work sheet (Worksheet for Primary Reviewer), to ensure that inadvertent omissions do not occur in considering the conformity of the application to all criteria for approval of research, and that a proposed continuation date and special monitoring requirements are identified. The work sheet will itemize the eight criteria for approval of research upon full review listed in the **RESPONSIBILITIES** Section (Section II.A.), and include additional items on the following: proposed interval until next continuation review, to be based on the estimated extent of risks (longest interval one year); whether or not the written informed consent document is sufficiently informative and includes all elements of informed consent, and whether and what kind of revisions in the protocol or consent document have been or need to be obtained for the application to be approved.

Primary reviewers for projects undergoing continuing review will have *access to all protocol-related materials including amendments to the protocol, revised consent documents, relevant correspondence (with sponsors and/or IRB), adverse events (adverse effects, protocol violations and/or deviations, physical or psychological harm, breaches of confidentiality or privacy, etc.), safety reports (IND, IDE, Medwatch) and reports from Data Safety Monitoring Boards, if any. A summary of all actions, including excerpts from prior IRB minutes, will be included in the Protocol History generated by the MIRB database.* Primary reviewers also receive a copy of the "Continuing Review Progress Reports: Reviewers Checklist" to complete as part of their review. This checklist consists of two parts: the first part is completed by the IRB Office, and the second part is completed by the Primary Reviewer. The IRB Office review (part one) determines if the PI has responded to all questions, that the consent document submitted is the most current, and that the PI has indicated that correct informed consent procedures were used. The in-depth reviewer completes the second part, which includes: 1) whether all changes in methods or purpose have been reviewed and included in the project as amendments; 2) whether all adverse events, unanticipated problems involving risks to subjects, subject withdrawals from the study, subject complaints, etc. have been reported; 3) if any recent literature, findings or relevant information, especially about risks associated with the research, have been submitted and reviewed by the IRB. Upon completion, the in-depth reviewer must answer whether approval is recommended for this project to continue and recommend an approval period up to a maximum period of one year.

Prior to distributing the materials to reviewers and other IRB members, the IRB Office will have the authority to request from the applicant investigator, revisions or additional information or documents in order to have complete and accurate information available for the IRB reviews. Prior to the IRB meeting to discuss the project, the primary reviewer(s) will have the authority to request from the applicant investigator, via the IRB office, revisions or additional information or documents. Upon completing his/her review, the primary reviewer will present the project to the

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IRB membership, at a meeting of the IRB, the agenda of which includes the project. Each member of the IRB, whether a primary reviewer or not, has the ability to comment on each project, and to recommend changes in the protocol and in the consent document. If a member of the IRB is an investigator or co-investigator or has any other potential conflict of interest on a project being discussed, he/she is excused from the meeting during discussion and voting on that particular proposal.

Following presentations by the reviewers, and after sufficient discussion, the members will vote on the new project application, to approve it, disapprove it, or defer a decision until revisions are implemented, additional information is provided, or further expert review is obtained (including invitation of ad hoc reviewers). All such motions must be carried by the majority of the voting members present at that meeting. In the case of approvals, the motion must indicate the length of time for which this approval is given. This period cannot exceed 12 months. Similarly, for continuing review progress reports, a motion will be made to provide full approval, to approve it pending minor revisions, to disapprove the report and suspend the project until further information is received, or to terminate the project. The approval motions must also indicate the length of approval granted (12 months or less, as appropriate). Similar motions are made for requested modifications and amendments to approved protocols. However, the date of approval of an amendment/revision does not change the date by which the regularly scheduled continuing review of the project is to be completed.

In general, the IRB will base the length of approval upon degree of risk to the subject population. Projects considered to be of high risk will be approved for periods of less than one year. The IRB may also recommend shorter approval times for protocols from junior and/or inexperienced investigators who may need closer supervision, for pilot studies in which it is possible that preliminary results may change the future direction of the study, or where it would appear that, for example, one year's worth of subject accrual may not be necessary.

In the case of motions that include requests for major revisions, responses to various questions, etc., investigators must submit their revisions and/or responses for full review at a subsequent IRB meeting. Unless there is a need for an ad hoc reviewer, the IRB Office will assign the same primary reviewers who provided the initial reviews.

If the convened IRB approves research contingent on specific minor conditions, the IRB Chair or another IRB member designated by the Chair, may approve the revised research protocol on behalf of the IRB. The date of approval is the date the fully-convened IRB approved the protocol rather than the date that the minor changes were approved by the IRB Chair, or designee. The research may not begin until the IRB Chair, or designee, has approved the changes and the R&D Committee has approved the research. The approval by the Chair, or designee, must be documented in the minutes of the first IRB meeting that takes place after the date of the approval. The revised protocol and/or consent document will be available for review by IRB members at this meeting or at any time, if desired.

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Following review of an adverse reaction, a motion will be made, as appropriate, for disposition of the issue (e.g., issue noted with no further action at this time, request for additional details, approval of modified consent document, motion to discontinue project, etc.).

Calculation of protocol expiration: The date of IRB approval of a study is used to determine when continuing review must be performed. Calculation of protocol expiration date will be based on the date of the convened meeting at which the IRB approved the protocol or approved the protocol with modifications. A protocol expiration date will be the last date that the protocol is approved. This is interpreted specifically as the date given for expiration at midnight (ex: 04/15/2008 at 12:00 a.m.).

a. **Convened IRB Review.** If the convened IRB procedure is employed, the continuing review date is determined by the date the convened IRB reviewed and approved the study.

(1) **No Conditions.** If the convened IRB approves the study with no requirement for modifications, the date of approval is the date of the convened IRB meeting at which approval was granted.

(2) **Minor Conditions.** If the convened IRB approves the study contingent on specific minor modifications to the protocol or the informed consent form, the study cannot proceed until subsequent review and approval of the materials submitted in the investigator's response to the minor conditions specified by the convened IRB. The IRB Chair, or an experienced IRB voting member designated by the Chair, may use expedited review procedures to verify that the specific minor conditions were met. The date of approval for the purpose of determining the date of continuing review is the date the study was approved by the convened IRB contingent on minor conditions being addressed.

(a) Investigators must be notified in writing when the IRB Chair or designated IRB voting member has approved the minor conditions.

(b) The approval of minor conditions by the Chair or designated IRB voting member must be documented in the minutes of the first IRB meeting that takes place after the date of the approval of the minor conditions.

(3) **Substantive Conditions.** If the convened IRB defers approval of a study contingent on substantive modifications or clarifications to the protocol or the informed consent form, the convened IRB must review and approve the investigator's modifications. The date of approval is the date the substantive modifications or clarifications were approved by the convened IRB.

b. **Expedited Review.** If the expedited review procedure is employed, the date of continuing review of the research study is based on the date the IRB Chair, or experienced IRB voting member(s) designated by the IRB Chair, gives final IRB approval to the research study.

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2. Minutes of the IRB Meeting.

Minutes of the IRB meeting must be written and once approved by the members at a subsequent IRB meeting; the minutes must not be altered by anyone, including a higher authority. Minutes of IRB meetings must contain sufficient detail to show:

- The presence of a quorum throughout the meeting including the presence of one member whose primary concern is in a non-scientific area. A detailing of attendance at the meetings will be recorded, to include when members arrive, when members leave early, when members step out of the meeting temporarily (and when they return), and when members are excused because of conflicts of interest (and when they return).
- Attendance at the meeting will also be documented for those members or alternate members who are participating through videoconference or teleconference, and documentation that those attending through videoconference or teleconference received all pertinent material prior to the meeting and were able to actively and equally participate in all discussions.
- Alternate members attending the meeting and for whom they are substituting.
- Actions taken by the IRB including those involving full initial review, continuing review, amendments, AEs, and SAEs. The IRB also uses the minutes to notify IRB members of actions taken through expedited review and to notify IRB members of stipulations met and final approval letters issued for protocols previously reviewed and approved with minor contingencies.
- Documentation of the four required findings (36 CFR 16.116(d)) when approving a consent procedure that does not include or that alters some or all of the required elements of informed consent, or when waiving the requirement to obtain an informed consent.
- The vote on actions including the number of members voting for, against, and abstaining.
- A note indicating that when an IRB member has a real or potential conflict of interest relative to the proposal under consideration, that the IRB member was not present during the deliberations or voting on the proposal (and that the quorum was maintained).
- The basis for requiring changes in or disapproving research and documentation of resolution of these issues when resolution occurs.
- A written summary of the discussion of controverted issues and their resolution.
- Review of additional safeguards to protect vulnerable populations if entered as study subjects when this is not otherwise documented in IRB records.
- The determination of the level of risk, if not recorded elsewhere in IRB records.
- The frequency of continuing review of each proposal as determined by the IRB if not recorded elsewhere in the IRB records.
- Documentation, as required by 45 CFR 164(i)(2), indicating the approval of a waiver or alteration of the HIPAA Authorization.

3. R&D Committee Review of IRB Actions.

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The IRB minutes are completed within 3 weeks of the IRB meeting date and once approved are then distributed to members of the R&D Committee. IRB Actions (including any protocol which has received full IRB approval with no remaining contingencies) are reviewed at the next scheduled meeting of the R&D Committee for ratification of the committee's actions. The R&D committee can modify IRB actions and request further review, but CANNOT approve a project that has been disapproved by the IRB. Human studies research on an IRB approved project cannot start until final approval by the R&D Committee.

G. REPORTING OF IRB DECISIONS

1. Reporting to Investigators.

If the IRB's motions on a protocol are ratified by the R&D Committee, then the IRB chairman shall complete a Report on Subcommittee on Human Studies form (Form 10-1223), indicating the IRB's action (approve, disapprove, revise). This form will be sent to the investigator along with additional information specific to the type of IRB action that was taken.

a. Notification for Actions of Approval. For approval actions, the following forms will be sent to investigators along with Form 10-1223:

Notice of Approval. The Notice of Approval form indicates the date of IRB approval, length of approval, and date of expiration of approval. This form also summarizes the responsibilities of the investigator with respect to timely submission to IRB of protocol-related materials (protocol changes, adverse reactions, closure and termination notices), the medical records requirements, and the need for timely submission of the continuing review progress report, including an indication of when the progress report must be submitted to the Research Office and an indication of the penalties if not submitted by that date. This form also indicates that the investigator will be given advanced warning of this deadline.

Approved Consent Document. The original of the approved consent document is sent to the principal investigator as the official document for copying and use in the study. This approved document is stamped with an approval date and expiration date on each page and initialed by the Chair, IRB on each page. For amendments or changes to consent documents, the approval date is the date of approval of the change in the consent document, while the expiration date is the date of the last complete review of the total project.

b. Notification For Actions of Disapproval And/or Revision. For disapproval actions, the following notification procedures will be utilized along with Form 10-1223:

Advanced Notification. Projects that are disapproved and/or require major revision before possible approval will receive advanced notification before the review by the R&D committee to allow the investigators maximum time to make revisions for resubmission, if desired, for the next meeting of the IRB. Such notification will be made by telephone and/or e-mail message by the IRB Administrator within 5 days after the IRB meeting. Investigators will also be provided with

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a written copy of the recommendations and motions of the IRB, including modifications required to secure IRB approval of the research activity. Disapproved research activities will also receive statements of the reasons for the IRB's decision. In all cases, if they wish, investigators will have the opportunity to discuss the actions with the IRB Chairperson and/or ACOS for R&D, and/or file an appeal in writing for additional review at the next or other subsequent IRB meetings.

Formal Notification. If the IRB's motions are ratified by the R&D Committee, then investigators will also receive an R&D approval letter.

2. Reporting of IRB Decisions to Other Services at the VA.

a. Reporting of Research Activities to Authorities Within the Medical Center and VACO. The R&D Committee Meeting minutes, which contain a full copy of that month's IRB meeting minutes (as well as copies of the minutes of other subcommittees that met that month), are provided to the Chief of Staff for review and to the Medical Center Director through their membership in the R&D Committee. Copies of the draft minutes are then forwarded to the membership of the R&D Committee for comments or corrections and formal ratification at the next month's meeting of the R&D Committee. When approved (with corrections, etc.), the minutes are then distributed to all PIs, and forwarded to VA Central Office (upon request). These minutes are also available at any time, upon request, from the Research Administration Office.

b. Reporting Decisions to Pharmacy Service. To assure full cooperation between the Research Service and the Pharmacy Service, a representative of the Pharmacy Service sits on the IRB as a permanent voting member. Thus, through this representative, the Pharmacy Service has input to and knowledge of all IRB actions that involve both approved and investigational drugs. To insure that Pharmacy Service has all the necessary information for control of investigational drugs, the PI will make available to the Pharmacy Service the following items following approval of the project:

- the IRB approval form,
- a complete copy of the master protocol and/or local protocol,
- a copy of the final approved version of the consent document, and
- a signed copy of Investigational Drug Information Record (if appropriate).

H. VHA HEALTH RECORD

A VHA health record must be created or updated, and a progress note created, for all research subjects (Veterans or Non-Veterans) who are admitted to VA facilities as in-patients, treated as

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outpatients at VA facilities, or when research procedures or interventions are used in the medical care of the VA research subject at a VA facility or at facilities contracted by VA to provide services to Veterans (e.g., contract CBOCs or contract nursing homes) (see VHA Handbook 1907.01).

a. **When a Health Record is Required.** A record must be created:

(1) When the research requires use of any clinical resources, such as: radiology, cardiology (e.g., electrocardiogram, stress test, etc.), clinical laboratory, and pharmacy; or

(2) If the research intervention may lead to physical or psychological AEs (see VHA Handbook 1907.01).

b. **What a Health Record Must Include.** At a minimum, the health record must include the following information for an approved research study:

- (1) The name of the study;
- (2) The person obtaining the subject's informed consent;
- (3) A statement that the subject or the subject's LAR was capable of understanding the informed consent process;
- (4) A statement that the study was explained to the subject or the subject's LAR;
- (5) A statement that the subject or the subject's LAR consented before participation in the study began;
- (6) A statement that the subject or the subject's LAR was given the opportunity to ask questions;
- (7) A copy of the signed and dated research informed consent form (i.e., VA Form 10-1086) in accordance with VHA Handbook 1907.01;
- (8) A copy of the HIPAA authorization for data use or disclosure (see VHA Handbook 1907.01);
- (9) A copy of the initial enrollment progress note and other applicable progress notes (see VHA Handbook 1907.01);
- (10) Information on possible drug interactions and/or toxicity of the pharmaceutical agents that are being administered to the subject because of the research (i.e., investigational drugs) (see VHA Handbook 1907.01);
- (11) VA Form 10-9012, Investigational Drug Information Record, or superseding forms for investigational drugs as defined in VHA Handbook 1108.04 (see VHA Handbook 1907.01);
- (12) A copy of any research results that are used for medical care (see VHA Handbook 1907.01);
- (13) Information on all research and experimental interventions including potential risks, indications, and applicable progress notes see (see VHA Handbook 1907.01); and

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(14) VHA Form 10-3203, Consent for Use of Picture and/or Voice, if applicable

c. **Identifying Research Clinic Visits.** A method to identify clinic visits solely for research (such as a note title) must be used to differentiate those visits from any other clinic visits.

d. **Non-Billing Events.** Clinic visits and inpatient care for research purposes must be coded as non-billing events (see VHA Handbook 1907.01).

e. **When Access to Patient Health Records is No Longer Required for a Study.** When access to patient health records is no longer required for a study, the study has been completed, or when authorization is revoked, the investigator or designee, must enter a research study closure addendum to the study initiation note.

I. FLAGGING A VHA HEALTH RECORD

The IRB may determine that the patient health record must be flagged to protect the subject's safety by indicating the subject's participation in the study (see VHA Handbook 1907.01).

a. Mandatory Flagging

(1) The patient health record must be flagged if the subject's participation in the study involves:

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

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

b. **Flagged Health Record Contents.** If IRB determines and documents that the patient health record must be electronically flagged in Computerized Patient Record System (CPRS) as participating in a research study then, in accordance with VHA Handbook 1907.01), the health record must:

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(1) Identify the investigator, as well as contact information for a member of the research team that would be available at all times. *NOTE: The research team must have an appropriate member available (on-call) at all times.*

(2) Contain information on the research study or identify where this information is available.

c. **Duration of Flagging.** The duration of flagging is in accordance to Medical Center Professional Memorandum 11-13 Medical Records Standards

All electronic research progress notes originally written by a clinical research coordinator (study coordinator) must be co-signed by the PI.

**For additional information please see the HRPP Training – CPRS notes guidance.*

J. SPECIAL REQUIREMENTS FOR PROJECTS INVOLVING INVESTIGATIONAL AND CLINICAL TRIAL DRUGS.

1. General Policy.

It is Medical Center policy, as delineated in MEDICAL CENTER MEMORANDUM NO. 1, Section 4, Pharmacy Service 119-01, that all experimental agents must be kept in and dispensed directly to the patient from the Pharmacy Service, and not by the investigator. Such medications will be dispensed only for a project that has been through the full approval process as outlined above. Exceptions may be made for life-threatening situations in accordance with approved Medical Center policies as discussed in MEDICAL CENTER PROFESSIONAL MEMORANDUM 11-221--Use of Investigational and/or Clinical Trial Drugs. Such exceptions may be made on a case-by-case basis only, may not be used to circumvent the approval process, and any results obtained from such emergency patient use may not be used as valid research data. The following criteria will apply for the emergency use of a test article (e.g., investigational drug or biologic): [1] The subject is facing a life-threatening situation, in which there is no standard acceptable treatment available, or in which conventional treatments have failed, [2] The physician has legitimate access to a test article, and believes that there is a reasonable likelihood that it may be helpful in the life-threatening condition, [3] There is not sufficient time to get approval by the IRB, and [4] The subject to receive the test article will not be enrolled in a research study involving the test article employed. *If it is not feasible to obtain informed consent, then it also must be certified in writing that a) informed consent cannot be obtained from the subject because of an inability to communicate with, or obtain legally effective consent from the subject, and b) time is not sufficient to obtain consent from the subject's legal representative. Approval is obtained from the Chief of Staff who will act as a second, independent physician who is not otherwise participating in the clinical investigation and finally,*

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from the Chairperson, IRB, following a formal joint written request by the attending physician and Chief of Staff. In accordance with FDA regulations listed in 21 CFR, Chapter 1, Section 56.104C (4-1-97 Edition) for emergency use of a test article, the IRB needs to be notified in writing within 5 days of a Medical Center approval of a life-threatening exception. Since such exceptions may not be used to circumvent the approval process, if subsequent use of the test article is contemplated in the same subject or in others, a new project application for the protocol must then be submitted to the IRB for full review in advance of that use. No additional patients may be added under the protocol without IRB approval.

An exception may also be made for patients who are admitted to the VA Medical Centers while they are receiving investigational drugs through an approved research protocol from another facility, if there is not sufficient time to obtain IRB review and approval. Such patients may not receive these drugs until such time that the Chief of Staff and Chair, IRB have given approval for their continued use at the Medical Center. Approval will not be given until contact is made with the principal investigator at the other facility and all local clinicians are informed adequately as to the protocol. As with life-threatening exceptions, the IRB needs to be notified within 5 days of a Medical Center approval of treatment under an approved protocol from another facility. Since such exceptions may not be used to circumvent the approval process, if subsequent treatment is contemplated in the same subject or in others, a new project application for the protocol must then be submitted to the IRB for full review in advance of that use. No additional patients may be added under the protocol without IRB approval.

2. Specific Procedures for Dispensing Drugs.

VA human research involving investigational drugs must be conducted in accordance with all applicable VA and other Federal requirements including, but not limited to Handbook 1200.05, VHA Handbook 1108.04, FDA regulations and this policy. This applies to investigator conduct and IRB review and approval of investigational drug studies, as well as storage and security procedures for investigational drugs. If the research involves FDA-regulated drugs, both VA requirements and FDA regulations apply. FDA regulations supersede VA requirements for human subjects research under FDA jurisdiction unless VA requirements are more restrictive than applicable FDA regulations.

a. **Investigational New Drug (IND) Application.** An IND application must be submitted to FDA for a clinical investigation on products that are subject to section 505 of the Food, Drug, and Cosmetic Act or to the licensing provisions of the Public Health Service Act (58 Stat. 632, as amended (42 U.S.C. 201 et seq.) unless the clinical investigation meets the exemption criteria set forth in 21 CFR 312.2(b).

b. **Investigator Responsibilities.** To receive an investigational drug as defined by VHA

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Handbook 1108.04, in addition to FDA regulations for the conduct of research under an IND and investigator responsibilities the investigator must:

(1) Provide the Pharmacy Service or Research Investigational Pharmacy information on each subject receiving an investigational drug through the electronic medical record or other locally approved means. Documentation is to include allergies, toxicities, or adverse drug events related to the investigational drug, or the potential for interaction with other drugs, foods, or dietary supplements, i.e., herbals, nutraceuticals (see VHA Handbook 1108.04).

(2) Ensure the local Pharmacy Service or Research Service Investigational Pharmacy receives:

- (a) Documentation of IRB and any other relevant approvals;
- (b) A copy of VA Form 10-9012, Investigational Drug Information Record, when applicable;
- (c) A copy of the current approved protocol;
- (d) A copy of the informed consent form for each participating subject with all appropriate signatures;
- (e) Documentation of the IRB continuing review approval;
- (f) Copies of sponsor-related correspondence specific to the drug(s) as appropriate;
- (g) Copies of all correspondence addressed to the investigator from the FDA (and other involved authorities) specific to the investigational drug(s) as appropriate;

(3) Inform the Chief of the Pharmacy Service, the research pharmacy when applicable, and the IRB in writing when a study involving investigational drugs has been suspended, terminated, or closed;

(4) Comply with all dispensing requirements; For each specific patient for whom the medication has been prescribed, the investigator or an authorized study prescriber, must submit an electronic drug order using CPRS. The electronic drug order must comply with all VA policies and procedures. *Under no circumstances will prescriptions be filled that are ordered by practitioners other than the PI or authorized study prescribers.*

(5) Comply with all documentation requirements and make relevant records accessible to the investigational drug pharmacist when requested (VHA Handbook 1108.04 6.a.(4));

(6) Comply with all VHA pharmacy requirements regarding receiving, dispensing, storing, and record-keeping for investigational drugs.

c. **IRB Review.** When an IRB reviews a study involving a drug, whether or not the drug has been approved by the FDA, the IRB's review and approval of the study must comply with

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applicable FDA, VA, and other Federal requirements including, but not limited to, VHA Handbook 1200.05, 21 CFR 56, and 21 CFR 312.2(b)(1). Investigators are prohibited by local policy from conducting research involving Investigational Device Exemptions at the Syracuse VA Medical Center. It is also noted that classified research involving human subjects cannot be approved by a VA facility IRB or affiliate IRB or Research and Development Committee or performed at VA facilities.

When reviewing a study involving a drug the IRB Pharmacy Representative(s) or designee as determined by the IRB Chair confirms that:

- (1) The drug has a valid IND; or
- (2) The protocol meets one of the FDA exemptions from the requirement to have an IND.
 - Exemption 1
 - The drug product is lawfully marketed in the United States.
 - The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug.
 - If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product.
 - The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.
 - The investigation is conducted in compliance with 21 CFR 50 and 56.
 - The investigation is conducted in compliance with the requirements of 21 CFR 312.7.
 - Exemption 2
 - A clinical investigation is for an *in vitro* diagnostic biological product that involves one or more of the following:
 - Blood grouping serum.
 - Reagent red blood cells.
 - Anti-human globulin.
 - The diagnostic test is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure.
 - The diagnostic test is shipped in compliance with 21 CFR 312.160.
 - Exemption 4
 - A clinical investigation involving use of a placebo if the investigation does not otherwise require submission of an IND.

K. INVESTIGATIVE ROLE OF THE IRB.

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1. Range of Investigative Authority of IRB.

The IRB reserves the right, at its discretion, to monitor the above processes for any or all of the projects it has approved. It has the specific authority to observe or have a third party observe the consent process and the research itself. It has the authority to review patient records to make sure that the necessary documents, as required, are placed in the patient's records, that the patient is indeed eligible for such study, and any other details of the research that may be deemed pertinent.

Any procedural or protocol violations which are found will be brought to the attention of the Chair IRB, the ACOS for R&D, the investigator, appropriate institutional officials, and to the IRB.

2. Suspension/Termination.

The IRB will suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Following review and determination, the IRB will report promptly to the appropriate VA Medical Center committees (e.g., P & T Committee), the cooperative group and/or sponsor of the research and/or the FDA, all instances of serious or continuing noncompliance with federal regulations or determinations of the IRB. In addition, aside from temporary administrative holds, the IRB will report promptly to appropriate committees, sponsors and regulatory agencies all suspensions and terminations of IRB approval along with reasons for such actions. The IRB may suspend or terminate approval for any of the following reasons:

a. The investigator fails to:

- obtain informed consent
- retain completed consent form(s)
- make IRB required revisions prior to starting the study
- make IRB requested changes in the study
- provide accurate progress reports regarding the conduct of the study i.e. number of subjects, adverse reactions, etc.
- inform the IRB that the sponsoring agency has discontinued the study for reasons of safety

b. The investigator shows lack of propriety or deceit through:

- evidence that the original study has been altered
- unauthorized modification of the study or consent form
- scientific misconduct involving risks to human subjects or others
- evidence that the rights of subjects have been violated

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For additional information see R&D SOP 151-07

c. Careful review of reports of adverse events show that unexpected or serious harm occurred to subjects.

d. Significant new findings developed during the course of the research, which alter the feasibility of the study.

This suspension or termination may occur during the progress of a study or prior to the onset of a study. The investigator will be informed in writing of the suspension or termination, and a copy of the letter will be sent to the appropriate affiliated institutions (OHRP, FDA, ORO). All terminations of FDA regulated trials, initiated by the IRB, by mandate, must be reported to the FDA.

NOTE: *For suspended research, enrollment for new subjects cannot occur; continuation of research interventions or interactions in already enrolled subjects should only continue when the IRB or IRB Chair, in consultation with the Chief of Staff (COS), finds that it is in the best interest of individual subjects to do so.*

Specifically the IRB Chair, with appropriate consultation with the COS ordering the suspension or termination will:

- *Considers actions to protect the rights and welfare of currently enrolled subjects.*
- *Consider if the subjects may continue in the research.*
- *Considers whether procedures for withdrawal of enrolled subjects take into account their rights and welfare (e.g., making arrangements for medical care outside of a research study, transfer to another researcher, and continuation in the research under independent monitoring).*
- *Considers informing current subjects of the termination or suspension.*

Once notified of the suspension, the PI must immediately submit to the IRB Chair a list of research subjects for whom suspension of the research would cause harm.

If the study is FDA-regulated, the COS and IRB Chair must follow FDA requirements in 21 CFR 56.108(b)(3) in making their decision.

The sponsoring agency, private sponsor, ORD, ORO, or other Federal agencies must be informed, as appropriate.

Once suspended, IRB review and re-approval must occur prior to re-initiation of the research.

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3. Ongoing Investigative Procedures.

Currently, the IRB, Pharmacy Service and the Chief of Staff perform four such investigative processes:

a. Project Tracking. Through the use of a computerized data base system, the review status of all approved projects can be monitored on a daily basis. As noted previously, those projects that are not in compliance with the need for continuing review can be flagged and reported at the next IRB meeting. If a continuing review progress report has not been received by that meeting, the project will be subject to the procedures outlined previously.

b. Continuing Review of Consent Documents. At the time of continuing review: the IRB requires the investigator to supply the latest version of the consent document used in that project. This controls for the possibility that the investigator may be using a faulty or unapproved document. The PI is also required to submit a copy of each subject's signed consent document. These documents are reviewed by IRB staff, and kept in a separate sub-folder within the project file, all of which is in a locked file cabinet in the IRB Administrator's secured office.

c. Pharmacy Review of Requests for use of Experimental Agents. The Pharmacy Service will reject any and all applications for the use of experimental agents that are not conducted in compliance with the rules noted above. The Pharmacy Service is empowered to refuse all unauthorized use of such medications and to report to the IRB Chair and ACOS for R&D any investigator who attempts to use such medications without compliance with regulations.

d. R&D and Pharmacy Review of Drugs used in Research: From time to time, there are spot checks of all areas within the Medical Center for the presence of unauthorized experimental agents or drugs. Such items, if found, are impounded by the Pharmacy Service, and the responsible investigator involved will be required to respond to the Physician Executive and to a fact-finding inquiry board to explain their presence in the Medical Center.

4. Appeal Process.

The appeal process is designed to find errors or uncover special circumstances that might alter the IRB's decision to suspend, disapprove or terminate a project. An investigator may appeal the following IRB actions:

- Disapproval of a proposal
- Termination or suspension of a proposal for the reasons outlined in Section I.2.

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The appeals process will consist of the following:

- a. The investigator will submit a written appeal request to the IRB within 30 days of receipt of the dated letter of disapproval, suspension or termination of the project. In this letter of appeal, the investigator must provide written justification for the appeal and submit new information for review.
- b. Upon receipt of the appeal, the request will be considered at the next IRB meeting. The investigator will be invited to the meeting to present the appeal and to answer questions.
- c. The investigator will be required to leave the meeting following the presentation and will be informed that written notification of the IRB's decisions will be forthcoming in a timely manner.
- d. The IRB will discuss the investigator's presentation and either approve or disapprove the investigator's appeal. A majority vote (>50%) by eligible voting members present is required for approval of the appeal. If the appeal is upheld, the investigator may initiate or continue the project subject to the restrictions or conditions approved by the IRB. If the appeal is denied, the project will be suspended or terminated.
- e. The IRB's decision is final.

L. RECORD KEEPING IN THE RESEARCH OFFICE.

The IRB Office will keep full records of all activities of the IRB. All IRB records are maintained in locked filing cabinets within locked rooms. Only authorized personnel have access to these records. The IRB controls access to its protocol files by tracking who, other than IRB members and office staff, accessed the files, by noting what files were accessed, by noting when the files were accessed and by identifying the purpose for access. All of these records shall be retained in accordance with the VHA Records Control Schedule (RCS 10-1). The official research file is a permanent record, which is maintained by VHA for 30 years after cut off of the records (cut off being the end of the fiscal year in which the study closed) and then transferred to the National Archives and Records Administration (NARA).

a. IRB STUDY FILE

The IRB records consist of all copies of all: research proposals reviewed; scientific evaluations, if any, that accompany the protocols; approved informed consent forms; progress reports submitted by investigators; and reports of injuries to subjects (38 CFR 16.115(a)(1)). The IRB protocol file must contain copies of all items reviewed including, but not limited to, all

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versions of:

- (1) Research Protocols.
- (2) Investigator's Brochures, if any.
- (3) Recruitment Materials, if any.
- (4) Scientific Evaluations, if any, which accompany the protocols.
- (5) IRB-Approved Informed Consent Forms.
- (6) HIPAA Authorization Documents (or documentation of waiver of HIPAA authorization).
- (7) Any Proposed Amendments and the IRB Action on Each Amendment.
- (8) Progress Reports Submitted by Investigators for Continuing Review.
- (9) Reports of Internal or Local SAEs (injuries to subjects).
- (10) Report of Unanticipated problems involving risk to participants or others.
- (11) Documentation of Protocol Deviations.
- (12) Documentation of Non-Compliance With Applicable Requirements.
- (13) Audit Results and Documentation of Compliance With Remediation Requirements.
- (14) Significant new findings. Statements of significant new findings provided to subjects as required in 16.116(b)(5) (38 CFR 16.115(a)(7)).
- (15) Subject complaints.
- (16) Summaries of Data Monitoring Committee Findings/Reports.
- (17) Communications/Correspondence with the investigator, including, but not limited to applicable:
 - a. Documentation of all relevant approvals,
 - b. Documentation of waiver of HIPAA authorization, and
 - c. Documentation of waiver of informed consent or waiver of documentation of informed consent.
- (18) Correspondence between the IRB and R&D Committee regarding the protocol.

2. IRB MINUTES

Draft minutes of IRB meetings must be written and available for review within 3 weeks of the meeting date. Once approved by the voting members at a subsequent IRB meeting, the minutes must be signed by the IRB Chair, or a qualified voting member of the IRB designated by the Chair. The final minutes cannot be altered by anyone, including other authorities or committees (e.g., the VA facility Director, RCO, Privacy Officer or ISO, or the R&D Committee). Minutes of IRB meetings must be in sufficient detail to document:

- a. **Attendance.** Attendance at the meetings includes those members or alternate members who participated through videoconference or teleconference; and documentation that those who

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attended through videoconferencing or teleconferencing received all relevant material prior to the meeting and were able to actively participate in all discussions.

b. **Quorum.** There must be the presence of a quorum for each vote, including the presence of one voting member whose primary concern is in a non-scientific area. *NOTE: This quorum, including the presence of one voting member whose primary concern is in a non-scientific area, could be indicated in the minutes by tracking attendance. It does not have to be indicated with each vote.*

c. **Alternate Members.** If applicable, document the presence of alternate members attending the meeting and for whom they are substituting.

d. **IRB Actions.** Document actions taken by the IRB.

e. **Vote.** Document the vote on these actions including the number of voting members voting for, against, and abstaining.

f. **IRB Member Conflict of Interest.** When an IRB member has a potential, actual, or perceived conflict of interest relative to the proposal under consideration, document the IRB member was not present during the deliberations or voting on the proposal, and that the quorum was maintained. *NOTE: "Not present" means that an IRB member must leave the room or, if participating in the meeting by conference call or videoconference, must have terminated the connection.*

g. **IRB Determinations and Justifications**

(1) Document determinations made by the convened IRB when those determinations are required by applicable VA and other Federal requirements.

(2) Document protocol-specific findings justifying those IRB determinations for:

- (a) Waiver or alteration of the informed consent process in accordance with 38 CFR 16.116(c) and (d); or (38 CFR 16.117(c);
- (b) Research involving pregnant women;
- (c) Research involving prisoners; and
- (d) Research involving children.

NOTE: The minutes must specifically document that the IRB determined that all criteria for waiver or alteration of the informed consent process were met.

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(3) If an IRB uses an expedited review process, these determinations and protocol-specific findings justifying those IRB determinations must be documented in either the IRB protocol file or the minutes.

h. **Vulnerable Populations.** Document any review of additional safeguards to protect vulnerable populations if entered as study subjects and findings related to the use of surrogate consent.

i. **Subjects Susceptible to Coercion or Undue Influence.** Document that safeguards are adequate to protect the rights and welfare of subjects who are likely to be susceptible to coercion or undue influences.

j. **Risk and Rationale.** Document the IRB's determination of the level of risk (e.g., whether or not the research constitutes minimal risk) and the rationale for the IRB's determination of the level of risk.

k. **Informed Consent Requirements.** Document the IRB's determination that all appropriate elements were included in the informed consent form, and are included in the informed consent process. In studies using an informed consent form, the form must include appropriate blocks for signatures and dates.

l. **Frequency of Continuing Review.** Document the IRB's determination of the frequency of continuing review of each study.

m. **Changes or Disapproval.** Document the basis for requiring changes in or disapproving research.

n. **Controverted Issues.** Provide a summary of the discussion of controverted issues and their resolution.

o. **Significant New Findings.** Provide statements of significant new findings.

p. **Non-Veteran Subjects.** Provide a summary of the justification for including non-Veterans as subjects .

q. **Real Social Security Numbers.** Provide a summary of the discussion when real Social Security Numbers (SSNs), scrambled SSNs, or the last four digits of SSNs will be used in the study. The summary needs to include the security measures that are in place to protect the SSN instances embedded in the study. *NOTE: This does not apply if the only use of SSNs is on the informed consent form or the HIPAA authorization as required by VHA Handbook 1907.01).*

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M. CREDENTIALS AND TRAINING

All VA research staff (clinical and non-clinical) conducting human research (exempt or non-exempt) must be credentialed and privileged (if applicable) as required by current local, VA, VHA (see VHA Handbook 1100.19), and ORD requirements. Research staff (including volunteers) may only perform those activities in a research study for which they have the relevant:

a. **Credentials.** Each member of the research staff must be appropriately credentialed, except individuals providing secretarial support who should undergo the Human Resource Management (HRM) process for administrative personnel.

b. **Privileges**

(1) If the local facility where the research is to be performed requires privileging to perform a given duty (e.g., a procedure) in the clinical setting, the individual must be privileged at that facility to perform the duty before the individual can perform that duty in the research setting.

(2) If the local VA facility requires privileging to perform a given procedure, it is not sufficient for only the supervisor of the person performing the research procedure to be privileged for that procedure. The person actually performing the research procedure must be privileged for the procedure.

c. **Research Scope of Practice or Functional Statement.** Each member of the research team must have a Research Scope of Practice Form or Addendum to the Clinical Functional Statement that has been approved by the individual's immediate supervisor and the ACOS for R&D, and that defines the duties the person is allowed to perform for research purposes. A research scope of practice statement or functional statement must be developed for all research personnel (clinical and non-clinical) who are not privileged for all the duties the person is allowed to perform for research purposes. The research scope of practice statement or functional statement must be consistent with the occupational category under which the individual was hired, and it must not include any duties for which the individual is not qualified. Current scopes of practice for all non-privileged research personnel must be retained by the Research Office.

NOTE: *A duty (e.g., a procedure) cannot be added to a scope of practice statement or functional statement, unless the individual meets all criteria to perform the duty in the clinical setting (e.g., the individual must be privileged for a procedure if privileging is required for that procedure in the local clinical setting).*

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(1) If research personnel are involved in more than one study, the research scope of practice statement or functional statement may be written to cover multiple studies (i.e., personnel do not need a research scope of practice statement for each protocol).

(2) If an employee's clinical privileges, clinical scope of practice statement, or clinical functional statement includes all of the duties necessary for a specific research study (e.g., taking a medical history, drawing blood, performing a muscle biopsy, ordering and interpreting laboratory tests), an addendum to the Clinical Functional Statement should be completed for research purposes.

d. **License, Registration, and Certification.** The employee must have all required licenses, registrations, or certifications to perform a given procedure, intervention, or other activity in the research setting and practice only within the scope allowed by such licenses, registrations, or certifications.

N. STUDENT AND OTHER TRAINEE RESEARCH

a. Research Conducted by Students and Other Trainees to Fulfill Academic Requirements.

Only students and other trainees (including residents and fellows), including VA employees, from schools with an academic affiliation agreement consistent with current VHA policy, may serve as investigators within a VA facility, or use data, or human biological specimens that have been collected within VA for clinical, administrative, or research purposes. **NOTE:** *A waiver may be obtained from the CRADO under special circumstances.*

(1) A VA investigator sufficiently experienced in the area of the trainee's research interest must serve as PI or co-PI and is responsible for oversight of the research and the trainee. The PI or co-PI is responsible for ensuring the trainee complies with all applicable local, VA and other Federal requirements.

(2) In conducting the research, the trainee must comply with all VA and other Federal and local institutional requirements, including those related to research, information security, and privacy.

(3) If the trainee does not complete all aspects of the research prior to leaving VA, the VA employee serving as the PI or co-PI must ensure the protocol is completed or terminated in an orderly fashion, and in accordance with all applicable local, VA, and other Federal requirements.

(4) When the trainee leaves VA, the VA employee serving as the PI or co-PI is responsible for ensuring all research records are retained by VA.

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O. TISSUE BANKS:

Per VHA Directive 200-043 (Banking of Human Research Subjects' Specimens, (dated 11/6/2000, memorandum distributed 3/28/2001), a separate file will be maintained by the ACOS for R&D for all new banks within the facility. These records will include the location of the bank and the name of the investigator responsible for the oversight of the bank.

P. RESPONSIBILITIES OF INVESTIGATORS

The PI must uphold professional and ethical standards and practices and adhere to all applicable VA and other Federal requirements, including the local VA facility's SOPs, regarding the conduct of research and the protection of human subjects. The responsibilities of the investigator may be defined in the protocol or IRB application. Specifically, the PI's responsibilities include, but are not limited to: **NOTE:** *Some of the following responsibilities may be assumed by an investigator working under a PI.*

a. **Disclosing Conflicts of Interests.** This means disclosing to the IRB any potential, actual, or perceived conflict of interest of a financial, professional, or personal nature that may affect any aspect of the research, and complying with all applicable VA and other Federal requirements regarding conflict of interest.

b. **Ensuring Adequate Resources.** This means ensuring there are adequate resources to carry out the research safely. This includes, but is not limited to, sufficient investigator time, appropriately qualified research team members, equipment, and space.

c. **Ensuring Qualified Research Staff.** This means ensuring research staff are qualified (e.g., including but not limited to appropriate training, education, expertise, credentials and, when relevant, privileges) to perform procedures assigned to them during the study. In a protocol, study team members are generally identified by name or by title.

(1) The Syracuse IRB requires specific individual(s) be listed by name as part of the study team as a condition for IRB approval of the research. Any proposed change in that specific individual's responsibilities requires IRB approval.

d. **Promptly Reporting Changes in PI.** This means promptly reporting any changes in the PI to the IRB. These changes include, but are not limited to, additions to or loss of staff. Changes in the PI, LSI, Co-PI, or Co-LSI of an IRB-approved project must be evaluated and approved by IRB to ensure the new individual meets the criteria described in 38 CFR 16.111.

e. **Overseeing the Research Staff.** This means overseeing and being responsible for ensuring

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the research staff under the investigator's direction comply with all applicable requirements including, but not limited to, implementing the research study in accordance with the approved protocol.

f. **Ensuring Complete Information in Research Protocol.** This means ensuring the research protocol contains all required information.

g. **Obtaining Written Approvals.** This means obtaining written approval(s) before initiating research. Before initiating the research study at a given site, IRB approval must be obtained in writing from the Chair or other voting member of the IRB, and all other committees (e.g., R&D Committee), subcommittees, and other approvals according to applicable local, VA, and other Federal requirements.

(1) For a VA multi-site study, not only the PI, but also all LSIs, must obtain such approvals from the relevant local VA facilities' IRBs of record and all other local committees, subcommittees, and other approvals according to the respective applicable local, VA and other Federal requirements.

(2) Research cannot be initiated at any given site until the local investigator has obtained written notification that the research can be initiated from the local ACOS for R&D (see VHA Handbook 1200.01).

h. **Implementing the Study as Approved.** This means ensuring the study is implemented as approved by the IRB and in accordance with other required approvals and with all applicable local, VA, and other Federal requirements including, when applicable, those for research involving investigational drugs.

i. **Maintaining Investigator's Research Records.** This means maintaining written documentation on file that the protocol is being implemented as approved by IRB and in accordance with other required approvals.

(1) Research records include the following when relevant to the study:

(a) Copies of all IRB-approved versions of the protocol and amendments.
(b) Case report forms and supporting data, including, but not limited to, signed and dated informed consent forms and HIPAA authorizations.

(c) Documentation on each subject including, but not limited to:

1. Informed consent,
2. Interactions with subjects by telephone or in person,
3. Observations,

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4. Interventions, and

5. Other data relevant to the research study, including, but not limited to:

- a. Progress notes,
- b. Research study forms,
- c. Surveys, and
- d. Questionnaires.

(d) Reports of adverse events.

(e) Data analyses.

(f) Reports including, but not limited to, abstracts and other publications.

(g) All correspondence including, but not limited to, that with the funding source or sponsor, and with applicable oversight entities including, but not limited to, IRB, R&D Committee, ORO, and FDA.

(h) A master list of all subjects for whom informed consent has been obtained in the study

(2) Documents must be maintained so that they may be audited by the facility RCO or other entities according to applicable sponsor, local, VA and other Federal requirements, and

(3) An Accounting of Disclosure must be maintained for each and every disclosure of information from this study to a non-VA entity. *NOTE: The facility Privacy Officer can assist in providing a mechanism to account for this disclosure.*

j. **Obtaining Informed Consent.** This means ensuring that no human being is involved as a subject in research covered by this Handbook unless legally effective informed consent of the subject or the subject's LAR has been obtained (38 CFR 16.116). The informed consent must be obtained and documented prospectively (i.e., no screening or other interaction or intervention involving a human subject can occur until after the IRB-approved informed consent requirements have been met). The only exceptions are if the IRB of record determines the research is exempt (see 38 CFR 16.101(b)), or approves a waiver of informed consent (see 38 CFR 16.116(c) and (d), or approves a waiver of the signed informed consent form (see 38 CFR.117(c)).

(1) **Designating Responsibility for Obtaining Informed Consent.** If the PI does not personally obtain informed consent, the investigator must formally and prospectively designate to another research team member in writing the protocol or the application for IRB approval the responsibility for obtaining informed consent, whether or not a waiver of documentation of

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informed consent has been approved by the IRB. This designee must be a member of the research team.

(a) Any person designated to obtain informed consent must receive appropriate training and be knowledgeable enough about the protocol to answer the questions of prospective subjects.

(b) The PI does not have to designate the individual by name, but can designate the position(s) title in the protocol or the application for IRB approval.

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

(3) **Circumstances Under Which Informed Consent is Obtained.** The investigator, or designee, must seek informed consent only under circumstances that:

(a) Provide the prospective subject or LAR sufficient opportunity to consider whether or not to participate, and

(b) Minimize the possibility of coercion or undue influence.

(4) **Usual Care.** The investigator, or designee, must ensure the Informed Consent process clearly defines for the subject which potential risks are related to the research (see subpar. 10g and 38 CFR 16.116(a)(2)) and, therefore, must be discussed with the research team, versus those associated solely with usual care provided by the subject's health care provider. The informed consent process must include language advising subjects to review the risks of the latter with their health care providers.

(5) **Documentation of Informed Consent**

(a) When documentation of informed consent is not waived by IRB, the investigator or designee must ensure the documentation is in accordance with paragraph 33 of this Handbook and includes:

1. The signature and date of the subject or the subject's LAR, and
2. The signature and date of the person obtaining the informed consent, and
3. The signature of the witness and the date of the subject's or LAR's signature was witnessed, when applicable.

(b) If use of facsimile is approved by IRB, the subject may submit the signed and dated informed consent form to the investigator or designee by facsimile.

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(6) **Storage of Signed Informed Consent Forms.** The investigator must ensure all original signed and dated forms are in the investigator's research files, readily retrievable, and secure.

k. Ensuring Consistency of Informed Consent Form, Protocol, and HIPAA

Authorization. This means ensuring the language in the informed consent form is consistent with that in the protocol and, when applicable, in the HIPAA authorization.

1. Ensuring HIPAA Authorization is Obtained. This means ensuring that no human being is involved as a subject in research covered by this Handbook, unless the investigator or a designee formally and prospectively designated in writing in the protocol by the investigator has obtained legally effective HIPAA authorization for the use and disclosure of the subject's PHI, or has obtained Privacy Board or IRB (IRB serves as the Privacy Board)-approved waiver of HIPAA authorization.

(1) If the investigator requires a waiver or alteration of the HIPAA authorization, the investigator must provide the IRB with information sufficient for the or IRB to find that such waiver or alteration is necessary (VHA Handbook 1605.1).

(2) Investigators can obtain and use real Social Security numbers only when real Social Security numbers are required to meet the specific aims of the research protocol or to enter information into the subjects' health records. The collection and use of real Social Security numbers must be approved by IRB, and the investigators must follow all applicable VA and other Federal requirements for obtaining and using real Social Security numbers.

m. Performing Subject Outreach. This means ensuring that, as part of the local VA facility's Research Subject Outreach Program, the investigator is responsible for:

(1) Making every reasonable effort to make available the informational brochure, "Volunteering in Research – Here Are Some Things You Need To Know," (<http://www.research.va.gov/programs/pride/veterans/tri-fold.pdf>) to potential research subjects in settings where investigators may recruit subjects (e.g., clinic waiting areas), and to prospective subjects, and their surrogates where applicable, when the individuals are approached to take part in a study.

(2) Ensuring that all informed consent forms provide subjects with required contact information for the VA investigator and relevant study staff. In addition, all informed consent forms must provide a contact independent of the research team in case the research staff cannot be reached, and the subject wishes to talk to someone other than the research staff, or the subject wishes to voice concerns or complaints about the research.

(3) Informing the independent contact person who is independent of the research team (e.g., the facility's patient advocate, a member of the research office staff, or IRB staff) of the relevant details of the study; documenting that this independent contact person has been informed; and

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ensuring the independent contact person's ability to render proper assistance to potential subjects.

(4) Additional information can be found in R&D SOP 151-19.

n. **Ensuring Appropriate Telephone Contact with Subjects.** This pertains to contacting the subject by telephone. Research team members are prohibited from requesting Social Security numbers by telephone.

(1) **Initial Contact.** During the recruitment process, ensuring the research team makes initial contact with the potential subject in person or by letter prior to initiating any telephone contact, unless there is written documentation that the subject is willing to be contacted by telephone about the study in question or a specific kind of research (e.g., if the potential subject has diabetes, the subject may indicate a desire to be notified of any diabetes-related research studies). The initial contact must provide a telephone number or other means that the potential subject can use to verify the study constitutes VA research. *NOTE: One source of information about clinical trials that can be shared with potential subjects is the NIH clinical trials Web site (<http://www.clinicaltrials.gov>) where VA clinical trials are listed.*

(2) **Later Contact.** Ensuring the research team begins telephone calls to the subject by referring to previous contacts and, when applicable, the information provided in the informed consent form, and ensuring that the scope of telephone contacts with the subject is limited to topics outlined in IRB-approved protocols and informed consent forms.

o. **Obtaining IRB Approval for all Changes.** This means obtaining IRB approval for all changes to the research protocol (e.g., amendments or modifications), including changes to the IRB informed consent form (the IRB informed consent form is unique to each research study), prior to implementing the changes. The only exception is when it is necessary to change the protocol to eliminate apparent immediate hazards to the subject. The investigator must promptly report these changes to the IRB.

p. **Submitting Continuing Review Materials.** This means ensuring continuing review materials are submitted in a timely manner to provide IRB sufficient time for reviewing and approving the study before IRB approval expires. IRB approval automatically expires if the continuing review and approval does not occur by the expiration date of the current approval.

q. **Reporting Deviations and Complaints.** This means reporting deviations from the protocol and subject complaints to IRB.

r. **Reporting Problems and SAEs.** This means reporting all unanticipated problems involving risks to subjects or others, and all internal (i.e., local) SAEs, whether related or unrelated to the research, in accordance with local SOPs and VHA Handbook 1058.01. *NOTE: Current guidance on such reporting can be found on the ORO Web site*

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(<http://www1.va.gov/oro/>).

s. **Completing Appropriate Actions at Research Project Completion.** This means at completion of the research study, completing all required documentation and storing research records according to all applicable VA and Federal records retention requirements. If appropriate, the investigator communicates the results to subjects or the community from which subjects were recruited.

t. **Transferring of Records.** This means transferring of records by VA upon departure of the investigator. If the investigator leaves VA, all research records are retained by the VA facility where the research was conducted. If the grant is ongoing and the investigator leaves one VA facility to go to another VA facility, the investigator must obtain approval for a copy of relevant materials to be provided to the new VA facility's research office. The approval must be obtained from the first VA facility's research office, any other relevant individuals or offices according to VA and local requirements (e.g., compliance, privacy, or Information Security Officers (ISOs)) and the sponsor.

NOTE: The investigator is not the grantee, nor does the investigator own the data.

u. **Maintaining a Master List of All Subjects.** This means the investigator must maintain a master list of all subjects from whom informed consent has been obtained whether or not IRB granted a waiver of documentation of informed consent (see 38 CFR16.117(c)).

(1) Investigators must not add a subject's name to the master list of all subjects until after:

- (a) Informed consent has been obtained from that subject, and
- (b) When appropriate, informed consent has been documented using an IRB-approved informed consent form.

(2) IRB may waive the requirement for the investigator to maintain a master list for a given study if both of the following conditions are met:

- (a) There is a waiver of documentation of informed consent, and
- (b) The IRB determines that including the subjects on such a master list poses a potential risk to the subjects from a breach of confidentiality.

(3) If IRB waives the requirement to maintain such a master list, IRB must provide written documentation in the IRB minutes or IRB protocol file justifying the waiver.

(4) The investigator must secure the master list appropriately in compliance with all VA

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confidentiality and information security requirements in the investigator's file for each study.

v. **Ensuring Appropriate Research Laboratory Test Reporting.** This means ensuring research laboratories not report laboratory results that are used for diagnosis, treatment, and prevention of disease in patients, unless the research laboratories are properly accredited and meet all requirements of 42 CFR 493 (see VHA Handbook 1106.01).

w. **Ensuring Requirements of Multi-site Studies.** In addition to the requirements in listed above:

(1) The PI of the overall study in a VA multi-site study must submit a protocol to the IRB of record for the PI's facility that includes the following:

(a) A method for ensuring that all engaged participating sites have the most current version of the protocol, the most current version of the informed consent form, and the most current version of the HIPAA authorization.

(b) A method for ensuring that all required approvals have been obtained at each engaged participating site (including approval by the site's IRB of record) before the study is implemented at that site.

(c) A method for notifying the Director of any facility deemed by the PI's IRB of record not to be engaged in the research, but on whose premises research activities will take place, before initiating the study (e.g., the PI conducts a survey of employees at a facility that is not engaged in the research). The facility Director has the authority to disapprove the conduct of these research activities on that facility's premises.

(d) A method for confirming that all amendments and modifications to the protocol, the informed consent form, and the HIPAA authorization have been communicated to engaged participating sites, and that all required local facility approvals (including approval by the local facility's IRB of record) have been obtained before the amendment or modification is implemented.

(e) A method for assuring that all engaged participating sites will safeguard VA data as required by VA information security policies.

(f) A method for communicating to engaged participating sites SAEs that have the potential to affect implementation of the study.

(g) A method of communicating regularly with engaged participating sites about study events and interim results (if appropriate).

(h) A method for ensuring all LSIs conduct the study appropriately.

(i) A method to ensure all non-compliance with the study protocol or applicable requirements is reported in accordance with VHA Handbook 1058.01.

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(j) A method for notifying local facility directors and LSIs when a multi-site study reaches the point that it no longer requires engagement of the local facility (e.g., all subsequent follow-up of subjects will be performed by the PI from another facility).

(2) When the investigator is a LSI for a multi-site study (whether the LSI is also a PI or solely a Local Site Investigator), the LSI must:

(a) Conduct the study according to the most recently approved version of the protocol, the most recently approved version of the informed consent form, the most recently approved version of the HIPAA authorization, and all applicable local, VA and other Federal requirements;

(b) Ensure that all amendments and modifications to the protocol and the informed consent form are submitted to and approved by the local IRB of record prior to initiating any changes;

(c) Report any unanticipated internal or local SAEs, whether related or unrelated to the research, in accordance with VHA Handbook 1058.01;

(d) Report study events and interim results (if available) to the local IRB of record as required by local IRB policies; and

(e) Oversee all aspects of the study at their local site.

b. Local VA Facility's IRB of Record's Responsibilities for Multi-Site Research When the VA Facility's Investigator is the Multi-Site Study PI for All Participating Facilities and the VA Central IRB is Not Being Used . In addition to other IRB responsibilities delineated in this Handbook 1200.05, when the VA facility's investigator is the multi-site study PI or study sponsor for all participating facilities, and VA Central IRB is not being used, the PI's or study sponsor's local VA facility's IRB of record is responsible for:

(1) When a participating site is added to the study, determining:

(a) Whether or not that site will be engaged in human subjects research.

(b) If the site will be engaged in research, then reviewing and confirming that it:

1. Has an active FWA, and

2. Has provided documentation of all relevant approvals, including approval of its IRB of record.

(2) Approving the study-wide protocol and sample informed consent document to be provided to each LSI at engaged facilities.

(3) Ensuring the study-wide protocol contains a mechanism for ensuring that any differences in the protocol or informed consent at engaged local participating sites are justified by the LSI,

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and that they are approved by the PI before being implemented.

(4) Ensuring there are clear AE reporting requirements, a data monitoring committee if applicable (or other reliable monitoring mechanism) with clear procedures and requirements, and a clearly defined feedback loop to the PI's or study sponsor's IRB.

(5) Reviewing the PI's plan for communicating appropriate critical information (e.g., reports of data and safety monitoring) to engaged participating sites.

(6) Ensuring, when relevant, confidentiality and information security requirements are met for information storage at and transmission to statistical or coordinating centers.

(7) Reviewing reports from applicable DMCs.

10. RESEARCH PROTOCOL

The investigator is responsible for the research protocol, and therefore, is responsible for:

a. **Ensuring Research is Scientifically Sound.** This means the investigator ensures that the research is scientifically sound.

b. **Ensuring Research Compliance.** This means the investigator ensures that research is in compliance with all applicable local, VA, and other Federal requirements.

c. **Providing a Plan for Recruitment and Selection of Subjects.** The investigator provides a plan for just, fair, and equitable recruitment and selection of subjects. *NOTE: The requirement for a plan for just, fair, and equitable recruitment and selection of subjects applies to both prospective and retrospective studies, including studies that use clinical or administrative databases or bio-specimens.*

d. **Minimizing Risks.** This means the investigator is responsible for minimizing risks to the subjects or others.

e. **Describing Data and Safety Monitoring Plan for Prospective Studies.** This means the investigator describes the data and safety monitoring plan for prospective studies. This plan must include, but is not limited to, the following:

(1) What safety information will be collected including SAEs (see VHA Handbook 1058.01);

(2) How the safety information will be collected (e.g., with case report forms, at study visits, by telephone calls with subjects);

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- (3) The frequency of data collection including when safety data collection starts;
- (4) The frequency or periodicity of review of cumulative safety data;
- (5) If not using a DMC, and if applicable, statistical tests for analyzing the safety data to determine if harm is occurring;
- (6) Provisions for the oversight of safety data (e.g., by a DMC); and
- (7) Conditions that trigger an immediate suspension of the research, if applicable.

***NOTE:** The data and safety monitoring plan may vary depending on the potential risks, complexity, and nature of the study. The use of an independent DMC needs to be considered if there are multiple clinical sites, the study is blinded, interventions are high-risk, vulnerable populations are included, or when required by the funding organization, FDA, sponsor, or other relevant entity.*

f. Describing Data and Safety Monitoring Plan for Retrospective Studies. This means the investigator describes the safety and monitoring plan for retrospective studies, including studies involving pre-existing data and biological specimens. When applicable, the plan needs to include, but is not limited to, the following:

- (1) A discussion with the subject of potential study outcomes that may have an effect on the subject's health or well-being; and
- (2) A procedure to determine when and how to notify individual subjects or their health care providers of findings that may affect the subjects' health.

g. Differentiating Usual Care from Research. This means the investigator provides for usual care. If the protocol involves "usual care," the protocol must either include a narrative section or there must be a separate document in the IRB application that clearly differentiates the research intervention(s) from "usual care" (whether the "usual care" is limited to one "arm" of the study or is being delivered to all study subjects) (See subpar 9j(4)).

(1) When a study involves "usual care," in the protocol or a separate document in the IRB application the investigator must clearly designate the individual or entity (e.g., the appropriate research personnel versus the subject's health care provider) responsible for relevant aspects of both the research and the usual care.

(2) The subject needs to be able to identify which activity (e.g., treatment or service) is research, and which is usual care, and know who (the researcher or the subject's health care provider) is responsible for:

- (a) Explaining potential risks and benefits of the treatment or service to the subject;
- (b) Providing the treatment or service;

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- (c) Monitoring the treatment or service, as applicable;
- (d) Defining whether the adverse events result from usual care or research, as applicable;
- (e) Alerting the subject if there is a problem with the treatment or service (e.g., a newly discovered risk, a product recall); and
- (f) Documenting the subject's clinical course while receiving the treatment or service, as applicable.

***NOTE:** The researcher and the subject's health care provider may be the same individual. If they are different individuals, and the subject's health care provider is not involved in the research study, the health care provider is not considered to be a member of the research team.*

h. Enlisting Clinical Expertise. This means the investigator provides for clinical expertise. If the investigator is not a clinician, when appropriate, the protocol must have provisions for enlisting the services of a clinician with appropriate expertise and privileges to perform duties that may include, but not be limited to:

- (1) Reviewing the data, adverse events, and new study findings; and
- (2) Making required decisions to protect the health of the subject (e.g., stopping the participant's involvement in the study or determining when to notify the subject or the subject's health care provider of information that may affect the health of the subject).

i. Providing for Privacy and Confidentiality. This means the investigator provides for privacy and confidentiality. To facilitate review of the protocol by the Privacy Officer (see par. 38), the investigator must either dedicate specific sections of the protocol to privacy and confidentiality, or the investigator must develop an additional document that specifically addresses all privacy and confidentiality issues in the protocol; this becomes part of the IRB protocol file. The description needs to be sufficiently specific for the reader to understand how this requirement protects the subject's privacy and the confidentiality of the data. These procedures must be in compliance with all applicable VA and other Federal requirements.

j. Providing for Information Security. This means the investigator provides for an information security plan. To facilitate review of the protocol by the ISO, the investigator must either dedicate specific sections of the protocol to information security, or the investigator must develop an additional document that specifically addresses all information security issues in the protocol; it becomes part of the IRB protocol file. The plan must clearly identify and include, but not be limited to:

- (1) Whether or not individually identifiable information is to be collected or used;
- (2) How the data is to be collected or acquired;
- (3) Where the data (original and all copies) is to be stored and corresponding security

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systems;

- (4) How the data is to be transported or transmitted from one location to another;
- (5) Who is to have access to the data and how they are to access it (anyone who has access to the data is responsible for its security);
- (6) All entities or individuals outside VHA to whom the data is to be disclosed, and the justification for such disclosure and the authority (e.g., the HIPAA authorization);
- (7) Who is to have access and be responsible for the security of the information (e.g., the Coordinating Center, the statistician, and PI who has ultimate responsibility);
- (8) Mechanisms used to account for the information;
- (9) Security measures that must be in place to protect individually identifiable information if collected or used; and
- (10) How and to whom a suspected or confirmed loss of VA information is to be reported.

***NOTE:** The special sections of the protocol dealing with privacy and confidentiality, and with information security, may be combined.*

k. Providing Special Safeguards. This means the investigator provides for special safeguards. When applicable, the protocol includes a narrative section that:

- (1) Identifies any circumstances that may warrant special safeguards to protect the rights and welfare of subjects who are likely to be vulnerable including, but not limited to, those subjects who may be susceptible to coercion or undue influence; and
- (2) Describes appropriate actions to provide such safeguards.

l. Providing for Reuse of Data. This means the investigator, if the data may be reused in other studies, describes the research data repository in which the data are to be stored (see VHA Handbook 1200.12). There must be a research informed consent and a HIPAA authorization associated with the protocol unless these requirements are waived by the IRB. If the IRB does not waive the requirements then the informed consent and HIPAA authorization content must include language on the uses and disclosures of the data as defined in the protocol as well as information on how privacy and confidentiality will be maintained and how the data will be secured. If the creation and operation of the data repository is not included in the data collection protocol, there must be a separate IRB-approved protocol for the creation and operation of the data repository (see VHA Handbook 1200.12).

m. It is the investigator's responsibility to disseminate this policy to all research staff under his/her supervision.

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n. Investigators may at any time bring forward to the organization any questions, concerns, suggestions regarding the HRPP program or in regards to the IRB review process through the established R&D reporting structure as appropriate

o. SERIOUS ADVERSE EVENTS (SAEs)

a. **SAE Reporting.** The investigator must report all unanticipated internal or local SAEs, whether related or unrelated to the research, to the IRB as specified under R&D SOPs 151-17 and VHA Handbook 1058.01.

b. **IRB Responsibilities for SAEs.** A qualified IRB voting member reviewer (or alternatively, the convened IRB) must review the reports of internal or local SAEs, and must determine and document whether the event is serious, whether it is anticipated or unanticipated, and whether it is related, possibly related, or probably related to the research in accordance with VHA Handbook 1058.01.

(1) **Documentation of Whether or Not Action is Warranted.** After taking into account considerations including, but not limited to, whether or not the study still meets IRB approval criteria under 38 CFR 16.111 and 38 CFR 16.116 (such as whether or not the risks to subjects have changed; whether or not the risk to benefit ratio has changed; and whether or not this constitutes new information that needs to be given to the subjects), the qualified IRB voting member-reviewer (or the convened IRB) must document whether or not one of the following applies in accordance with VHA Handbook 1058.01:

(a) Immediate Action Warranted. Immediate action (e.g., suspension of activities; notification of subjects) is necessary to prevent an immediate hazard to subjects in accordance with VA regulations at 38 CFR 16.103(b)(4)(iii), and review by the convened IRB is needed; or

(b) No Immediate Action Warranted. Review by the convened IRB is needed, but immediate action to prevent an immediate hazard to subjects is not warranted.

(2) **Reporting to Convened IRB.** If the preceding determinations are made by a qualified IRB voting member reviewer, the determinations must be reported to the IRB at the IRB's next convened meeting in accordance with VHA Handbook 1058.01.

(3) **Reporting to the Facility Director.** If the qualified IRB voting member reviewer (or the convened IRB) determines that the AE is serious, unanticipated, and related, or possibly related, to the research, the IRB Chairperson must report the event to the VA facility Director as soon as possible, but no later than 5 business days after the determination (VHA Handbook 1058.01). The VA facility Director then has an additional 5 business days to report the event to ORO (VHA Handbook 1058.01).

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(4) **Informed Consent Modifications.** If it is determined that an informed consent modification is warranted, the convened IRB must determine and document in its records whether or not previously enrolled subjects must be notified of the modification and, if so,

- (a) When such notification must take place, and
- (b) How such notification must be documented (see VHA Handbook 1058.01).

c. **Adverse Events of Research-Related Clinical Care.** When subjects experience adverse events while undergoing clinical care that is part of a research study, the clinical care adverse events must be disclosed to subjects in accordance with current VHA policy.

p. No research investigator who is obligated by the provisions of the Syracuse VAMC Federal-Wide Assurance, any associated Inter-Institutional Amendment, or Non-institutional Investigator Agreement will seek to obtain research credit for, or use data from, patient interventions that constitute the provision of emergency medical care without prior IRB approval. A physician may provide emergency medical care to a patient without prior IRB review and approval, to the extent permitted by law. However, such activities will not be counted as research nor the data used in support of research.

q. If the investigator leaves the VA facility, the original research records must be retained at the VA facility.

Q. INVESTIGATOR IRB MEMBER AND OTHER HUMAN SUBJECT RESEARCH PERSONNEL TRAINING: R&D SOP 151-24

R. PROCEDURES FOR HUMAN STUDIES ACTIVITIES ADMINISTERED THROUGH THE CENTRAL NEW YORK RESEARCH CORPORATION.

The Central New York Research Corporation is a non-profit research corporation, incorporated in the State of New York, whose mission is to further the research and educational missions of the Syracuse VA Medical Center and its research affiliates. It is empowered to administer research grants from private foundations, drug companies, the NIH and other Federal Agencies, private donors, etc. All VA-affiliated staff are eligible to participate in these activities, whether salaried by the VA or not.

All grants administered through the Corporation must have prior approval from the IRB and the R & D Committee of the Syracuse VA Medical Center before they can be activated. Since the Corporation does not have its own IRBPHS, it has formally designated the Institutional Review Board at the Syracuse VA Medical Center as its IRBPHS. All studies reviewed by the IRB for

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the Corporation will use the same review and approval/disapproval process and forms as listed above. Corporation funded investigators are also required to conform to the same reporting requirements and VA regulations as listed above for continuing review progress reports, prompt notification of modification of protocols, adverse reactions, etc.

III. REFERENCES

"Protection of Human Research Subjects" Title 45 Code of Federal Regulations Part 46 (45 CFR 46), issued by the United States Department of Health and Human Services.

"Protection of Human Subjects" Title 21 Code of Federal Regulations Part 50 (21 CFR 50), issued by the United States Food & Drug Administration.

"Institutional Review Boards" Title 21 Code of Federal Regulations Part 56 (21 CFR 56), issued by the United States Food & Drug Administration.

"Investigational Drugs" Title 21 Code of Federal Regulations Part 312 (21 CFR 312), issued by the United States Food & Drug Administration).

"Investigational Devices" Title 21 Code of Federal Regulations Part 412 (21 CFR 412), issued by the United States Food & Drug Administration.

"Standards for Privacy of Individually Identifiable Health Information," also known as the Privacy Rule of the Health Insurance Portability and Accountability Act (HIPAA), Title 45 CFR, Part 160 and Subparts A and E of Part 164.

"Federal Policy for the Protection of Human Subjects", the "Common Rule" which represents a consolidation of related regulatory policies of all federal agencies, issued by the United States Department of Health and Human Services. Federal Register Part II, Dated June 18, 1991.

"Protecting Human Research Subjects: Institutional Review Board Guidebook," prepared by the Office for Protection from Research Risks of the National Institutes of Health.

"The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research", prepared by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1979).

OPRR Reports: Continuing Review-Institutional and Review Board Responsibilities, Number 95-01, Dated November 10, 2010. <http://www.hhs.gov/ohrp/policy/continuingreview2010.html>

MEDICAL CENTER PROFESSIONAL MEMORANDUM NO. 11-100 - Administration of Medications, Dated March 2007.

MEDICAL CENTER PROFESSIONAL MEMORANDUM 11-221—Use of Investigational and/or Clinical Trial Drugs, Dated December 2005.

MEDICAL CENTER PROFESSIONAL MEMORANDUM 11-13—Medical Records Standards, Dated July 2009.

RESEARCH & DEVELOPMENT SERVICE STANDARD OPERATING POLICY 151-05, Conflicts of Interest, Dated May 2007.

NETWORK MEMORANDUM 10N2-147-07 NETWORK 2 INFORMATION SECURITY INCIDENT REPORTING POLICY, Dated July 1, 2007.

VHA Handbook 1200.05, Requirements for the Protection of Human Subjects in Research, October 2010

VA Manual M-3, Part I, Chapter 15, “Misconduct in Scientific Research”, Dated July 12, 1993

VHA Directive 200-043, Banking of Human Research Subjects’ Specimens, (dated 11/6/2000, memorandum distributed 3/28/2001).

VHA Directive 2003-036, Credentials and Training of Employees Involved in Human Subjects Research, (dated July 7, 2003).

McGuire Dunn, Cynthia, M.D. & Gary Chadwick, PharmD., M.P.H. Protecting Study Volunteers in Research: Manual for Investigative Sites, 1999, Center Watch Publications.

IV. RESCISSIONS

RESEARCH & DEVELOPMENT SERVICE STANDARD OPERATING POLICY 151-02, Policies & Procedures with Human Subjects, Dated March 2011.



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