Carilion Clinic
Institutional Review Board

Standard Operating Procedures

Original Version Date: September 2007
Revised Version Dates: January 2008
March 2010
Current Version Date: March 2013

Table of Contents

Carilion Clinic

Standard Operating Procedures Manual

Original Date: September, 2007
Current Version Date: March, 2013

The Policies and Procedures in this manual have been reviewed and approved by the appropriate Institutional Officials noted below. Additional guidance can be found in the IRB Standard Operating Guidelines.

Daniel P. Harrington, M.D.
Vice President for Academic Affairs
& Institutional Official

Charles J. Schleupner, M.D.
Chair, Institutional Review Board

Charles A. Hite, M.A., C.I.P
Director, Biomedical and Research Ethics

INTRODUCTION

Carilon Clinic is committed to expanding and disseminating knowledge for the benefit of the people of Virginia and the nation. An important part of that commitment to knowledge is research of the highest quality on all aspects of the health and behavior of people, and such research is only possible through the participation of humans as research subjects.

Human subjects are partners and participants in research and a precious resource to Carilion Clinic. At Carilion Clinic, human subjects research is a privilege, not a right. Consistent with that philosophy, it is the mission of the Carilion Clinic Human Subjects Research Protection Program to provide that:

1. the rights and welfare of human subjects are paramount in the research process;

2. the highest standards of ethical conduct are employed in all human subjects research;

3. research investigators are properly trained in the ethical and regulatory aspects of research with human subjects;

4. research investigators deal honestly and fairly with human subjects, informing them fully of procedures to be followed, and the risks and benefits of participating in research; and

5. research using human subjects at Carilion Clinic conforms with all applicable local, state and federal laws and regulations and the officially adopted policies of the Clinic.

The purpose of this document is to assist members of the Carilion community in fulfilling the stated mission of human subject research. This document is intended for the use of the Institutional Review Boards (IRBs) at Carilion Clinic. This set of Standard Operating Procedures (SOPs) is directed to IRB chairs and members, the staff of Department of Biomedical and Research Ethics (DBRE) and other affiliated persons and includes policies and procedures applicable to these persons in their capacities with the IRB. Further guidance can be found in the IRB Standard Operating Guidelines (SOGs).

1. Ethical and Regulatory Mandates for the Protection of the Carilion Clinic Human Research Subjects Protection Program

The regulation of human subjects research by the U.S. Department of Health and Human Services (DHHS) is codified in 45 CFR 46. Because Subpart A of 45 CFR 46 has been adopted for human subjects research by many federal agencies it is known as the "Common Rule." The Common Rule requires that every institution performing federally supported human subjects research file an assurance of protection for human subjects. This research should be guided by the ethical principles espoused in the Nuremberg Code and the Declaration of Helsinki and should conform to the guidance documents described below:

1.1 The Belmont Report

The Belmont Report elucidates three ethical principles that should guide research:

• Respect for persons (applied by obtaining informed consent, consideration of privacy, confidentiality and additional protections for vulnerable populations);

• Beneficence (applied by weighing risks and benefits);

• Justice (applied by the equitable selection of subjects)

1.2 45 CFR 46

This regulation, published by the Department of Health and Human Services, codifies basic human subject protection measures.

1.3 21 CFR 50 and 21 CFR 56

These Federal Drug Administration (FDA) Regulations define consent requirements for the use of certain types of drugs in human subjects research.

1.4 Assurance and IRB registration process

Carilion Clinic, as an institution involved in biomedical and behavioral research, should have in place a set of principles and guidelines that govern the institution, its faculty, and staff, in the discharge of its responsibilities for protecting the rights and welfare of human subjects taking part in research conducted at, or sponsored by, the institution, regardless of the source of funding. Assurances applicable to federally supported or conducted research must, at a minimum, contain such a statement of principles, which may include an appropriate existing code, declaration, and/or statement of ethical principles as formulated by the institution. *The Belmont Report* serves as such a document for Carilion Clinic.

The *IRB Standard Operating Procedures* represents the written procedures provided for in Carilion Clinic's Assurance. Additional written guidance can be found in the IRB Standard Operating Guidelines.

2. ROLES IN THE PROTECTION OF HUMAN RESEARCH SUBJECTS AT CARILION CLINIC

2.1 The Institutional Official

The Institutional Official at Carilion Clinic, as designated by the President and CEO, is the Vice President for Medical Education.

It is the responsibility of the Institutional Official to oversee Carilion Clinic's compliance with federal regulations pertinent to human subjects research. The official document pledging this responsibility is called the Federalwide Assurance (FWA), approved by the Office of Human Research Protections (OHRP) at DHHS. Part of this assurance includes the development and adoption of policies and procedures for conducting human subjects research and the appointment of an institutional official to oversee this process.

The Institutional Official will:

1) Set the tone for an institutional culture of respect for human subjects.
2) Ensure effective institution-wide communication and guidance on human subjects research.
3) Ensure that investigators fulfill their responsibilities.
4) Facilitate participation in human subjects education activities.
5) Appoint the IRB members, Chair and Vice-Chair.
6) Provide the IRB with the necessary resources and staff.
7) Support IRB authority and decisions.

2.2 Department of Biomedical and Research Ethics (DBRE)

The Department of Biomedical and Research Ethics (DBRE) is the chief administrative office of the Carilion Clinic Human Subjects Research Protection Program. This office administers, supports, guides and oversees the work of the Carilion Clinic Institutional Review Boards (IRBs) to uphold ethical and regulatory standards and practices in human subjects research at Carilion Clinic. The Department of Biomedical and Research Ethics reports to the Institutional Official. As part of the Federalwide Assurance process an institution is asked to identify a "Human Protections Administrator" (HPA) to serve as the primary institutional contact person for the Office for Human Research Protections. The organization has designated the Director of DBRE to be the HPA for Carilion Clinic.

The responsibilities of the HPA will be divided between the HPA and sufficient staff to assure that the goals of Human Research Protection Program are fulfilled. The HPA will oversee duties in the following three areas: 1) Communication and Education, 2) Recordkeeping and Reporting, and 3) Monitoring and Oversight. The HPA shall serve as a voting member of the IRB.

2.3 Institutional Review Boards (IRBs)

The IRBs are established by and fall under the aegis of Carilion Clinic. The IRB is an appropriately constituted group that the Clinic has designated to review and monitor research involving human subjects. The Clinic's IRBs are multiple panels with expertise required for the review of the Clinic's widely varied human subjects research studies. Within this document, the term "the IRB" is used to refer to all Clinic IRBs.

2.4 Principal Investigator (PI)

The principal investigator is the individual responsible for the implementation of research, and, as such, must personally conduct or supervise the research. The PI is responsible for ensuring that the research study is accurately and completely submitted for IRB review, that IRB approval is obtained prior to initiation of research or before making any changes or additions to the research; that the IRB is informed of all changes in information previously presented to the IRB; that progress reports are submitted to the IRB as required; and that all unanticipated problems or serious adverse events involving risk to human subjects are reported to the IRB. The PI is also responsible for ensuring that all members of the research team comply with the findings, determinations, and requirements of the IRB, including adequate performance of the informed consent process.

The role of PI implies administrative and fiscal responsibility as well as sufficient expertise for the research study. The PI has ultimate administrative and fiscal responsibility for the project, subject to Clinic review and oversight.

2.5 Research team members

Every member of the research team is responsible for protecting human subjects in accordance with the guidelines specified in 1.0, and for complying with all IRB findings, determinations and requirements. Team members must complete human subjects research training as required by the Carilion Clinic IRB.

2.6 Other Clinic reviewer bodies

In addition to Carilion Clinic IRB review, Carilion Clinic human subjects research studies may be reviewed by other Clinic committees and individuals charged with responsibility for evaluation of specific component research compliance issues. These may include one or more of the following:

- DBRE compliance personnel
- Institutional Biosafety Committee
- Radiation Safety and Lab Safety program personnel
- Institutional Privacy and Security Officers
- Contract and grant personnel in the Research Department
- Data Safety Monitoring Board
- Department level review committees

The factual information, evaluations and recommendations of these research review units may be very useful to the IRB's consideration of the rights and welfare of human subjects within the context of the specific Carilion Clinic research study. The Carilion Clinic IRB retains final responsibility and authority to approve each Clinic research study that involves human subjects.

3. IRB MISSION AND AUTHORITY

3.1 Scope and purpose

The purpose of the Carilion Clinic IRB is to protect the rights and welfare of human research subjects. To achieve this, the IRB must advise investigators in designing research projects in a manner to minimize potential harm to human subjects, review all planned research involving human subjects prior to initiation of the research, approve research that meets established criteria for protection of human subjects, and monitor approved research to ascertain that human subjects are indeed protected.

The IRB also informs and assists Carilion Clinic and its researchers on ethical and procedural issues related to the use of human subjects in research; facilitates compliance with relevant regulations of the United States Government; and provides a framework suitable for continued support by Government agencies, private foundations and industry for research involving human subjects at Carilion Clinic.

3.2 IRB responsibilities and authority

All human subjects research carried out at Carilion Clinic or under its auspices must be reviewed and approved by the IRB or determined exempt by DBRE prior to the involvement of human subjects in research.

The Carilion Clinic IRB reviews human subjects research: (1) sponsored by the Clinic; (2) conducted by or under the direction of any employee or agent of the Clinic in connection with his or her institutional responsibilities; (3) conducted by or under the direction of any employee or agent of the Clinic using any property or facility of the Clinic; or, (4) involving the use of Carilion Clinic non-public information to identify or contact human subjects.

Review and approval by an outside, central IRB may be used for certain multi-center research studies under the terms of a written agreement approved and signed by the Institutional Official for Carilion Clinic and the appropriate signatory official for a central IRB. Such an agreement must describe the responsibilities of each IRB and the process to be used for such review. The agreement must assure that Carilion Clinic will have opportunity to review and monitor the local conduct of research and that the central IRB will respond to concerns raised by the Carilion Clinic IRB or other Carilion Clinic officials charged with protection of human research subjects. In all research involving central IRB review and approval, the Carilion Clinic IRB shall have authority to maintain a process to review local protocol violations and local serious adverse events or unanticipated problems and to receive notification of any determinations of local serious non-compliance or continuing non-compliance. In all research involving central IRB review and approval, the Carilion Clinic IRB shall have authority to 1) make

its own determinations of local serious non-compliance or continuing non-compliance 2) require local investigators to develop and implement corrective action plans and 3) suspend or terminate local research activities

The Carilion Clinic IRB must conduct initial and continuing reviews of research and report the findings and actions to the investigator and the institution. These reviews include: the review of all research involving human subjects at a convened meeting of the IRB (except research classified as exempt or evaluated in expedited review); the approval of research with the concurrence of the majority of IRB members; the evaluation of proposed changes in approved research protocols; and, the determination if any project requires verification from sources other than the investigator that no material changes have occurred since previous IRB review. In addition:

• The IRB has responsibility for oversight of all human subjects research that is not exempt from IRB review;

• The IRB must protect the rights and welfare of subjects according to 45 CFR 46, 21 CFR 50, and 21 CFR 56, as applicable.

• The IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities;

• The IRB shall have authority to 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. Any suspension or termination of approval shall include a statement of the reasons for the IRB's action and shall be reported promptly to the investigator and the Institutional Official. The Institutional Official will determine whether or not the action should be reported to appropriate federal regulatory agencies. If such a report is required, the Institutional Official or the Human Protections Administrator shall be responsible for all required institutional reports to sponsors and federal agencies.

• The IRB must report to the Institutional Official unanticipated problems involving risks to subjects and others or serious or continuing noncompliance by investigators. The Institutional Official or Human Protections Administrator shall be responsible for all required institutional reports to sponsors and federal agencies.

• The IRB must review all research projects involving human subjects before the involvement of human subjects may begin.

• The IRB shall have authority to monitor the activities in approved projects, including auditing of the informed consent process, surveying subjects and conducting routine or for-cause audits in order to verify compliance with approved research protocols and informed consent procedures.

• The IRB or DBRE shall have authority to determine if an activity constitutes human subjects research or exempt status research as defined in federal regulations.

• The IRB shall employ a review process which conforms to the Federal Policy for Protection of Human Subjects, the regulatory codes 45 CFR 46 of the HHS and 21

CFR 50, 56, 312 & 412 of the FDA, and the current assurance, between Carilion Clinic and OHRP.

3.3 Agreements to provide IRB review of research conducted by unaffiliated investigators

Occasionally Carilion Clinic may be asked to provide IRB review for investigators who are affiliated neither with Carilion Clinic nor with another institution that has an IRB. Circumstances in which this arrangement might be considered would typically involve a study based at Carilion Clinic in which the unaffiliated investigator is collaborating. It will generally not be considered appropriate to extend IRB oversight to research by unaffiliated investigators in which Carilion Clinic is not otherwise engaged.

All requests for Carilion Clinic to serve as the IRB of record for an unaffiliated investigator should be referred to the Director of DBRE. The Director of DBRE, in consultation with the IRB and the Institutional Official as appropriate, will determine whether the Clinic will agree to extend IRB oversight to the unaffiliated investigator. If the decision is that Carilion Clinic will provide IRB oversight for the unaffiliated investigator, the Director of DBRE will be responsible for executing an “Unaffiliated Investigator Agreement” documenting this arrangement in accord with the relevant Carilion Clinic signature delegation. In most instances this agreement will apply to a single research project; less often, to a defined group of studies involving the unaffiliated investigator. Copies of this documentation will be returned to the unaffiliated investigator, the responsible IRB and DBRE files.

3.4 Agreements for deferral of IRB review from one FWA institution to another

On some occasions when two FWA institutions are engaged in the same research study, it may be appropriate for one institution to rely on the IRB of the second for review and continuing oversight of that research. Circumstances in which this arrangement might be considered would typically involve studies primarily based at one institution, with somewhat peripheral involvement by investigators at the other. In effect, this constitutes a deferral of the right of review by the institution with lesser involvement, which retains responsibility for ensuring compliance with all IRB requirements.

An “IRB Authorization Agreement” is the form of agreement executed between the institutions to document this delegation of IRB oversight. Carilion Clinic may be either the institution deferring to another institution or the institution to which the IRB review is delegated. All requests for such delegations should be referred to the Director of DBRE. The Director of DBRE, in consultation with the IRB and the Institutional Official as appropriate, will determine whether the Clinic will agree to the deferral. If the decision is to agree to the IRB delegation, the Director of DBRE will be responsible for executing the agreement, in accord with the relevant Carilion Clinic signature delegation. Copies of this agreement will be filed with the IRB accepting responsibility for ongoing oversight, the IRB deferring, and the DBRE at Carilion Clinic.

References:
21 CFR 50

21 CFR 56
45 CFR 46.102(d),(f)
45 CFR 46.103
45 CFR 46.109
45 CFR 46.109(d)
45 CFR 46.110
45 CFR 46.113
Declaration of Helsinki
The Belmont Report

4. IRB Organization And Administration

4.1 IRB Structure

The Carilion Clinic IRB will be composed of one or more committees. Each committee will have the necessary membership and administrative support to review and approve protocols. The IRB Chair or Vice-Chair for each committee will conduct each meeting. Each committee will meet on a regular basis at a time and place convenient for its members. The meetings shall be frequent enough to handle the business of the IRB.

The Carilion Clinic IRB will conduct its business with the participation of the following persons: regular voting members, alternate voting members, institutional representatives, consultants and ad hoc reviewers.

4.2 Appointment of members

The Institutional Official appoints members to the IRB based upon the recommendation of the Director of DBRE in consultation with the IRB chair.

Prospective members will typically be identified by the IRB chair and IRB staff, who should review the nature and demands of IRB service with the candidate. Recommendations and endorsements will be forwarded to the Institutional Official, who will issue the official letter of appointment.

IRB members are appointed for a three-year term, renewable for successive three-year terms without limit at the discretion of the Institutional Official.

4.3 Appointment of the chair and vice-chair

The Institutional Official appoints the IRB chair and vice-chair based upon the recommendation of the Director of DBRE in consultation with the outgoing IRB chair and the prospective chair's unit head.

Typically, but not necessarily, the IRB chair is selected from among sitting members of the IRB. The chair should be an individual with credibility and standing in the institution to command respect among the research community and the IRB, and one who is committed to the protection of human subjects in research. IRB chairs and vice-chairs are appointed for three-year terms which may be renewed for successive terms without limit at the discretion of the Institutional Official.

Whenever the Chair is not available, the Vice-Chair will assume the responsibilities of the Chair during the period of his/her absence. Whenever the Vice-Chair is not available, the Director of DBRE will assume the responsibilities of the Chair during his/her absence. The chair, vice-chair or Director of DBRE will have signatory authority for IRB minutes, approval letters, and other documents relating to IRB business. Signatory authority may be granted to designees as outlined in the IRB SOGs.

4.4 Regular Voting Members

Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. Each IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution. Additionally, each IRB shall include at least one member who is not a scientist. The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas.

Scientist members of the IRB will be recruited from active faculty or medical or clinical staff of Carilion Clinic or from staff of other area medical facilities. Non-scientist members will have had expertise in human rights issues and/or ethical or legal issues considered to be relevant to human subject research, and will be recruited from employees of Carilion Clinic or staff of other area medical facilities.

The standards described above represent *minimum* requirements which the Carilion Clinic IRB typically exceed. In many instances, an IRB will have ten or more members with varied expertise and specialization in order to meet the research review requirements of that IRB. Appropriate size of the IRB will be determined by the IRB Chair in consultation with the Institutional Official (IO) and the Director of DBRE.

When a protocol involving prisoners is reviewed the IRB must include at least one member with appropriate background and experience to serve as an advocate for the prisoner population. For protocols involving children the IRB review must include either a panel member or a consultant with expertise relevant to the participation of children in the study.

IRB membership is recorded on a roster that is submitted to the Office for Human Research Protections (OHRP).

4.5 Alternate members

Alternate members are appointed to the IRB according to the same procedures that apply to members. Alternate members serve when a voting member is not available. The alternate member must have background and expertise similar to the absent

member in order to serve for a scientist member. Alternate members with non-scientific backgrounds can serve in place of a non-scientist regular voting member.

4.6 Institutional Representatives

The IRB chair may, at his/her discretion, recruit institutional representatives from among the staff of Carilion Clinic. The presence of an institutional representative at the meetings of the IRB is intended to aid the IRB in conducting its duties. Institutional representatives are appointed to the IRB by the Institutional Official at the suggestion of the Chair and Director of DBRE. Institutional representatives may also be recruited and appointed at the discretion of the Institutional Official. Institutional representatives are appointed for a three-year term, which may be renewed, without limit. Institutional representatives may take part in all meetings of the IRB, participate in the discussions, and make recommendations, but they may not vote on the decisions. Institutional representatives are not included in determining or establishing a quorum at the meetings. IRB meeting minutes reflect the presence of institutional representatives.

4.7 Termination of appointment

Appointment to the IRB may be terminated before the expiration of the three-year term. The Institutional Official may remove an IRB member if the Institutional Official, in consultation with the IRB chair and Director of DBRE, determines that the member fails to perform his or her duties as a member.

When an IRB member leaves Carilion Clinic or the Roanoke area, or is otherwise unable to serve, he or she may voluntarily terminate his/her appointment. It is appropriate to give sufficient advance notice so that a replacement can be found.

4.8 Consultants

The Carilion Clinic IRB may, at the discretion of the chair or Director of DBRE, invite individuals with competence in special areas to assist in the review of issues that require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB. Consultants are not included in determining or establishing a quorum at the meetings. IRB meeting minutes reflect the presence of consultants.

4.9 Confidentiality agreement

Upon appointment to the IRB or attendance at an IRB meeting, members, institutional representatives, consultants, guests, and/or staff will sign a confidentiality agreement.

4.10 Education and training

IRB members as well as institutional representatives will be required to take educational training in human subjects research protections and pass an examination based on that training within three months of their appointment unless they have a current professional certification in research. They also will be asked to read the Belmont Report upon their appointment to the IRB. Videotapes, CDs, handouts, education conferences, workshops and in-services will be offered each year. After

three years of service to the IRB, members and institutional representatives will be required to complete additional educational training. Other educational training may be required at regular intervals.

The IRB, in conjunction with the Director of DBRE, will make available education and training materials and programs to researchers who have active research projects involving human subjects. All researchers and study coordinators who are not certified in research will be required to take educational training and pass an examination based on that training before being allowed to conduct research. Three years after completion of the initial training, investigators and study coordinators who are not certified will be required to complete additional educational training. Other continuing education may be required at regular intervals.

The educational training programs for IRB members and researchers and their staffs will be determined by the Director of DBRE in consultation with appropriate committees and oversight officials associated with the institution's human protections program.

4.11 Liability coverage for IRB Members

IRB members function as employees or agents of Carilion Clinic. As such their actions are covered by the Carilion Clinic liability coverage if taken within the course and scope of their employment or agency. This means that they are covered when performing within the course and scope of their IRB responsibilities.

Unaffiliated members of the IRB are also covered by Carilion Clinic liability coverage when performing within the course and scope of their IRB service.

4.12 IRB Meetings

The IRB will meet as often as necessary to process, without undue delay, the research project applications submitted for approval. With the exception of applications eligible for expedited review, the IRB membership will determine the outcome of its review of research project applications at meetings, where quorum has been established. Quorum requires the presence of the majority of the voting members of the IRB, including at least one of its non-scientist members. The approval of a project requires the vote of the majority of the members present at the meeting. If the quorum fails during the course of a meeting, a vote will not be taken unless quorum can be restored. The Chair, the Vice-Chair or, in their absence, the Director of DBRE, will chair the meetings.

Whenever a research project application is being reviewed in which a voting member, alternate member, institutional representative, consultant or guest may have a conflict of interest, that person will leave the IRB meeting for the duration of the review of that application and vote and will not participate in the discussion except to provide requested information.

Any member may abstain from voting for any reason that makes them believe that they are unable or unqualified to render a reasonable vote.

5. IRB REVIEW

5.1 General Information

It is the investigator's responsibility to submit to the IRB an application for review and approval of the project. No aspect of human subjects' research may begin until the IRB has granted the approval. The IRB will notify the investigator in writing of its findings or decisions for all types of review.

5.2 Types of Reviews and Submission Requirements

There are several categories of review that can take place. The exempt, expedited and full board approval reviews are determined by the federal regulations set forth in 21 CFR and 45 CFR.

To submit research to the IRB for review, there are certain items that will assist in understanding what is required in order to process research studies. See the Standard Operating Guidelines as a reference to specific submission requirements.

5.3 Initial IRB Review

In order to appropriately evaluate research an application for research will be required. The application and other required documents are described in the Standard Operating Guidelines.

The information may be pre-reviewed for completeness and compliance to Carilion Clinic policies by IRB staff or members. Also, in the case of drug or device studies, a literature search of information about the drug or device may be done.

Carilon Clinic IRB will use a primary reviewer system for the review of all protocol submissions. The primary reviewer system means that up to three members are assigned as special reviewers for each protocol to be reviewed at the full committee meeting. The primary reviewer(s) will be of sufficient number and expertise to adequately review the protocol. The primary reviewer(s) will review the study in detail and present findings at the meeting. The primary reviewer(s) will receive a copy of the Protocol Submission Application, the protocol, informed consent form, and, when applicable, the Investigator's Brochure, any relevant grant application(s), and other related information. The remainder of the IRB members will receive the Protocol Submission Application, which includes a protocol summary and the informed consent form.

At the IRB meeting, the Principal Investigator will be given the opportunity to give a brief presentation. There will be time to address questions from committee members. After this time, the Principal Investigator will be dismissed so the Board can continue their discussion and voting procedures.

There are basically four decisions the IRB may make regarding research:

1) Approve research as it is.
2) Approve research with some minor modifications.

3) Table research with recommendations for substantive clarifications or modifications.

4) Deny research.

During the IRB review process, additional information may be requested from the Principal Investigator.

The Principal Investigator will be notified by mail regarding the Board's decision. If the study requires minor changes to either the protocol or consent form, the letter will outline the changes necessary before an approval letter will be granted.

The approval of the protocol and consent will be valid for a twelve- (12) month period from the original approval date unless the IRB determines that the approval period should be shorter. The IRB may determine the approval period should be shorter if the protocol involves a high risk to patients or if there have been previous problems with the protocol or investigator.

5.4 Exempt

There may be some research activities which are exempt from the DHHS Federal regulations as listed in 45 CFR 46.101 (b) and (c). The DBRE or IRB will make a determination of whether these activities meet the criteria for exempt status.

5.5 Expedited

Expedited review may take place for research activities involving no more than minimal risk and for minor changes in approved research. Federal regulations define minimal risk as the probability that the magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

Research activities eligible for expedited review are limited by Federal Policy and FDA regulations and are listed in IRB Standard Operating Guidelines.

The expedited review procedure allows the review of the research by the IRB Chair or his/her designee. In conducting the review, these individuals may exercise all of the authorities of the IRB except that they may not disapprove the research. A research activity may be disapproved only subsequent to full board review. However, the reviewer reserves the right to choose not to expedite review of the research study. If full board review is required, the full IRB Review process must be followed.

If the review is expedited, a letter will be sent to the Investigator stating that the research has been approved in an expedited manner and the specific category justifying the expedited review. All items that are approved through expedited review will be noted in the agenda and minutes that IRB members receive.

It is not required that any research be expedited, and it is at the IRB Chairs' discretion to choose whether to expedite research or not. If the proposed research activity is not expedited, a letter will be sent to the Investigator explaining why the expedited approval was not granted.

5.6 Full Board

Research that does not meet the criteria for Exempt Review or Expedited Review must be submitted for Full Board Review.

The full review procedure allows the review of the research by one or more primary reviewers. The reviewers receive the complete study documentation for review, report to the IRB and lead discussion at the IRB meeting. If other members review summary information only, they must have access to complete study documentation. It is usually helpful that the person submitting the research be present at the IRB meeting to answer any questions that may arise. If the Principal Investigator or his/her designee is not available at the meeting, the IRB may postpone discussion.

5.7 Continuing Review Process

Continuing review refers to the process of re-assessment of all research studies. The purpose of continuing review is to ensure that the risk/benefit relationship is still acceptable, that the measures that have been taken to safeguard subjects are adequate, that the approved protocol is followed, and that the project reflects any changes that have been made in the regulations for human subjects research since the last approval.

Annual Continuing Review of all research protocols is mandatory (45CFR §46.109 (e) including research protocols in which human research subject accrual has been closed and the research interventions completed, but data continue to be collected and analyzed. The IRB may, however, require more frequent review or progress reports of certain research protocols based on a risk assessment.

Routine continuing review will include review of a written progress report from the investigator, the current consent document, and the current protocol. A primary/secondary reviewer system similar to the one used for initial review may be employed. When a primary/secondary reviewer system is used, the reviewers will receive a copy of the application, protocol and informed consent form, and the remaining members will receive a copy of the application, which contains a protocol summary and the informed consent form. The complete protocol file will be made available at the IRB meeting. The IRB may request verification from sources other than the researcher that no material changes have occurred since the initial or previous continuing review if:

1) the study is complex, involving unusual levels or types of risk to the subjects;
2) the researcher has failed previously to comply with the IRB's requirements or federal regulations; or
3) there exist reasons to have concerns about possible material changes occurring without IRB approval.

The IRB may take the following actions on any continuing review:

1) Approve the research as it is.

2) Approve the research with some minor modification.
3) Table the research with recommendations for substantive clarification or modifications.
4) Deny the research.

Continuing review of a study may not be conducted through an expedited review procedure unless the study was eligible for, and initially reviewed by an expedited review procedure or the study has changed such that the only activities remaining are eligible for expedited review.

The continuation of research after expiration of IRB approval is a violation of federal regulations. If the IRB has not reviewed and approved a research study by its expiration date, research activities should stop except where safety or ethical concerns demand they continue.

5.8 Changes

Any changes that need to take place in a research study must be approved by the IRB before those changes may be implemented. The only exception to this would be if those changes directly impact the safety of a research subject. Changes need to be submitted to the IRB. If the change qualifies for expedited review, it will be reviewed in this fashion by the IRB Chair or his/her designee. Otherwise, it will be reviewed by the full board at a convened meeting. The range of actions that the IRB may take on the change are:

1) Approve the change as it is.
2) Approve the change with some minor modifications.
3) Table the change with recommendations for substantive clarifications or modifications.
4) Deny the change.

5.9 Adverse Events and Unanticipated Problems

Any adverse event that is serious and unexpected and associated with the use of a drug or device must be reported to the IRB. These adverse events need to be submitted to the IRB in a timely manner. An adverse event is considered serious if it is fatal or life threatening; requires or prolongs hospitalization; produces a disability; or results in a congenital anomaly/birth defect. An adverse event is considered to be unexpected if it is not identified in nature, severity or frequency in the current IRB-approved research protocol or informed consent document.

The IRB also must review any unanticipated problem in a research study involving risks to subjects or others. Unanticipated problems must be related or possibly related to participating in a research study. An unanticipated problem suggests that the research places subjects or others at greater risk of harm than was previously known or recognized.

Reviews of serious adverse events and/or unanticipated problems are usually expedited by the IRB Chair or his/her designee, but may be presented to the full board for further evaluation if the reviewer determines it necessary. The IRB shall review any study that has been associated with unexpected serious harm to research subjects as soon as it is notified of the incident. The Chair may assign investigative responsibilities to any qualified person, or committee he assembles, and may request modifications to the protocol and/or consent form if it becomes apparent that risks or complications appear to be greater than those originally stated. The IRB also has the right to suspend or terminate the protocol in order to eliminate apparent immediate hazards to the subjects.

5.10 Non-Compliance/Complaints

The Carilion Clinic IRB has the responsibility to oversee the use of human subjects in research within its jurisdiction in order to protect the safety and welfare of the research subjects. The IRB shall investigate all allegations of non-compliance with human subjects regulations, which may originate outside of or within the IRB or DBRE. The IRB Chair will be informed of the allegations as soon as possible after they are made. He/she will use his/her discretion to assign investigative responsibilities to any one person or panel of qualified individuals. The chair also will decide if the accusation warrants immediate suspension of the protocol(s) in order to protect human subjects. The Principal Investigator will be sent written notice of the allegations and given the opportunity to respond.

Those assigned by the Chair to investigate any complaints or allegations of non-compliance will make every effort to complete the investigation in a timely manner. They will present the results of their investigation and recommendations along with any response from the investigator to the Chair. Again, he/she will determine if immediate suspension of the protocol(s) is warranted. The Chair may then make a decision to 1) dismiss the allegation or complaint as unjustified; 2) refer the matter to a more appropriate official, board or department; or 3) bring the matter to the IRB committee that originally reviewed the protocol for discussion and vote on action to be taken. The investigator will also be given the opportunity to attend the meeting in order to answer questions and address the board.

The IRB will provide in writing the results of its deliberation to the investigator, and, as required by regulations or ethics, will also notify any or all of the following entities of its findings and rulings:

1) the Office for Human Research Protections (OHRP)
2) the Food and Drug Administration (FDA)
3) external and internal sponsors
4) professional licensing boards
5) state agencies
6) department heads or medical directors

The IRB has the authority to suspend or terminate its approval of a research protocol that is not being conducted in accordance with regulatory or IRB requirements or that is associated with serious harm to human research subjects. Reasons for termination could include, but are not limited to the following:

- Failure to submit continuing reviews in a timely manner.
- Failure to comply with the policies outlined in this document.
- Failure to obtain and/or document that informed consent was obtained from subjects according to federal guidelines.
- Failure to submit changes to protocol and/or consent form prior to implementing those changes.
- Failure to maintain the educational requirements determined necessary by the IRB.

The Principal Investigator may request an appeal of his case be heard, but the request will only be granted under certain circumstances. These are 1) new information not reasonably available during the investigation; 2) material failure to follow these policies and procedures; and 3) the sanction exceeds the severity of the violations. The appeal will be heard by the IRB committee that made the original decision.

5.11 Reinstatement

Reinstatement and approval of a research project requires the approval of the IRB. The procedures for a new protocol submission must be followed for reinstatement of a suspended protocol.

5.12 Emergency Use of Non-Approved and Investigational Drugs

FDA human subjects regulations allow for a test drug to be used in emergency situations without prior IRB approval as long as the emergency use is reported in writing to the IRB within five (5) working days. Subsequent use of the test drug must be reviewed by the IRB. An emergency is defined as a life-threatening situation in which no standard acceptable treatment is available and in which there is not sufficient time to obtain IRB approval. The specifics of this process are outlined in the IRB Standard Operating Guidelines.

5.13 Vulnerable Populations

Basic ethical principles, as well as state and federal law, recognize that some groups of potential research subjects need special protection. These groups are composed of persons who are unable to fully participate in the decision to take part in research. These persons may lack mental capacity to assess the risks and benefits of research or they may be institutionalized in some manner that makes it impossible for them to make a voluntary decision to participate in research. These populations include children, prisoners, pregnant women and their fetuses. Other populations of potential research subjects need special protection due to health concerns or the special nature of the research. The Carilion Clinic IRB is committed to assuring that the rights of such

vulnerable populations are adequately protected whenever they are considered as subjects for human research.

Whenever a protocol involving a vulnerable population is submitted to the IRB, the committee will determine and document that it determined what level of risk is involved in the research, and follow applicable state and federal regulations in its deliberations.

6. INFORMED CONSENT

6.1 General

Subjects shall, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them; the informed consent process is the instrument to provide this opportunity. The IRB requires that the principal investigator of a research project obtain a legally valid informed consent from human subjects.

The informed consent process is different from the consent form. It involves meeting with a potential subject, finding out whether he or she is capable of giving consent, and discussing the purpose, risks, and benefits of participation. The consent form formalizes the agreement to participate and should be designed to document the process. Obtaining informed consent is not just giving a prospective subject a consent form and getting it signed.

If consent is to be informed, the subjects must genuinely understand the study. Researchers should strive to convey information to subjects, not merely disclose it to them. Subjects should be able to say what they are consenting to.

6.2 Documenting Consent with a Consent Form

Once a subject understands a study and has expressed a willingness to participate, researchers must document the subject's consent with a consent form. Although a dated signature certifies the subject's willingness to participate, it is not equivalent to assuring that the subject has understood the research. Including a date with the signature avoids confusion about whether the subject began to participate before giving informed consent. See the IRB Standard Operating Guidelines for specific requirements for consent forms.

6.3 Waiver of Informed Consent

In some circumstances, the federal regulations for human subjects' research allow a waiver of the requirement for informed consent. For example, a waiver is possible if a study investigates certain aspects of public benefit or service programs (see 45 CFR 46.116[c]). Also, either a waiver or a consent process that omits or modifies the essential elements of informed consent is possible if the IRB finds that:

- The research involves no greater than minimal risk to the subjects;
- The waiver or alteration will not adversely affect the rights and welfare of the subjects;
- The research would be impracticable without the waiver or alteration; and

- The subjects will be informed of the study when it is over (if at all possible).

Only the IRB can waive or modify the consent process. Researchers are not authorized to make this decision.

6.4 Waiver of Documentation of Informed Consent

The IRB may waive the requirements for a PI to obtain consent for some or all subjects if it finds either:

- That the only record linking the subject and the research would be the consent documents and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research and the subject's wishes will govern; or
- 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.

If the documentation requirement is waived, the IRB may require the PI to provide the subject with a written statement regarding the research.