

CARRICK INSTITUTE FOR GRADUATE STUDIES

INSTITUTIONAL REVIEW BOARD



STANDARD
OPERATING
PROCEDURE
MANUAL

THE CARRICK INSTITUTE'S INSTITUTIONAL REVIEW BOARD'S STANDARD OPERATING PROCEDURES MANUAL

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Chapter 1: The Purpose of an IRB:

A. Institutional Review Board (IRB) review and approval is required before initiating any research involving human subjects. The IRB is charged with the responsibility of protecting the rights and welfare of human subjects participating in research under the auspices of the institution with which it is affiliated. The Carrick Institute for Graduate Studies' program on human research protection is based on three basic ethical tenets of respect for persons, beneficence and justice and the application of these tenets set forth in the Belmont Report. The Carrick Institute for Graduate Studies will apply these tenants to all research done on human subjects regardless of funding.

Historical abuses have created the necessity of an IRB to oversee investigations involving human research stems from abuses that have occurred historically. Inhumane treatment of research participants by the Nazis while committing war crimes, were followed by the Tuskegee Syphilis study and cold war radiation experiments. Each of these led to guides such as the Nuremberg Code, the Declaration of Helsinki, the Belmont Report, HIPPA privacy rules and the publication of the common rule that were all designed to protect human research participants.

This manual is designed as a living document to assist the IRB chair, vice chair, members and investigators in the process of minimizing risk to the human research participant by following the three pillars from the Belmont Report of Respect for persons, Beneficence and Justice.

B. Additional Perspectives accomplished by protecting the research participant:

In addition to the primary purpose of the IRB in protecting human research participants, it should be noted that by protecting the participants there is additional value provided to the Carrick Institute.

I. Scientific knowledge:

The only way to advance the field of functional neurology among the academy is to publish. The IRB's role is to provide a foundation of safety for participants that the researchers can build quality studies upon. By assuring proper protections for human subjects in research, it enhances the trustworthiness of

the Institute to peer reviewers and editors of journals. Articles can be refused by journals if they perceive inadequate protections are in place.

II. Protect the Institution:

Consistent and thorough protections also shield the institute from liability that could come from injury to participants. Additionally, it protects the Carrick Institute from damage to its public image. As a foundation of evidenced based research in the field of functional neurology is built, it is critical that the "Brand" is protected. Quality IRB procedures help ensure this.

III. Protect the Researcher:

IRB members may feel "pressure" when reviewing a peer or mentor's research. Each IRB member should remember that in addition to protecting the research participant, they are also protecting the researcher.

The IRB must be and must be perceived to be fair and impartial, immune from pressure either by the institution's administration, the investigators whose protocols are brought before it, or other professional and nonprofessional sources. Therefore, IRB members should never succumb to outside pressures, but ensure appropriate protections are in order.

IV. Protect the IRB members:

Finally, by protecting the research participant, the IRB members are protecting the IRB Board itself and each of its members from unnecessary liability. Even though liability coverage may be present, proper protections for research participants and following fair guidelines for researchers minimize stresses and other hardships associated with legal actions.

Chapter 2: How to use this Manual

This manual is designed to serve multiple stakeholders. Those stakeholders include: IRB members, investigators, human research participants and other interested observers.

C. IRB Members:

This manual serves as an overview of how the IRB works including some of the “why” behind the rules and regulations to new members. It provides the new member with a working knowledge of the process and what will be expected of them.

For a new chair or vice chair this manual provides guidance to the history, pertinent laws and requirements for membership, along with a description of procedures and processes that they will oversee. This assures a continuity of professionalism that can be maintained over time with the change of various personnel within the board along with changes within the leadership.

D. Investigators:

Investigators may find value in the use of this manual because it gives them an understanding of the concerns IRB members will have, along with a description of the requirements the IRB members must adhere to. Additionally, by understanding thresholds for exempt review, expedited review and full review, the investigator may streamline their submission. This manual in essence, serves a map for the researcher to use as a guide to navigate through the institutional review process.

E. Participants:

Human research participants may use this manual to understand the standards and protections that will be in place if they choose to participate in research associated with the Carrick Institute. In this way they can be assured of the entire Institute’s commitment to their protection.

F. Interested Observers:

Journal editors, quality auditors and other interested observers may use this manual for their understanding of our processes and as a component of our assurances towards protection of our research participants and dedication to high quality scientific pursuits.

Chapter 3: Institutional Administration

I. Membership:

The IRB is composed of regular members. The IRB will, at times, invite individuals with expertise in special areas for consultation in the review. These individuals serve in an advisory capacity to the board but will not vote on the IRB submission. Carrick Institute's IRB, consistent with the federal mandates set forth by the US Department of Health & Human Services Code 45 CFR 46 and 21 CFR 56.107 makes every attempt to ensure they are sufficiently qualified through the experience and expertise of its members to review common types of studies submitted. This includes reviews involving vulnerable populations. The membership of the IRB is diverse, including considerations of race, gender, cultural backgrounds and sensitivity to community attitudes and values. The IRB also includes both men and women with scientific and nonscientific backgrounds and at least one individual who is not affiliated with the institution.

II. Record Keeping:

The IRB Office maintains a database of IRB committee members identified by name; earned degree(s); indications of experience such as board certifications, licenses, etc., sufficient to describe each member's primary anticipated contributions to IRB deliberations; representative capacity (e.g., scientific or non-scientific reviewer); and any employment or other relationship between the member and the Carrick Institute for Graduate Studies. The IRB Administrator will report changes in IRB committee membership to the OHRP within 90 days.

Formal meetings of the IRB will be recorded via Adobe Connect. Any PowerPoints or outlines of topics discussed will be maintained within this digital document, as will links and other materials shared.

III. Institutional Responsibilities:

I. FWA: Our Federal wide assurance requires:

1. All research approved for human participants is subject to the US Federal Policy for the Protection of Human Subjects (also known as the Common Rule). The Federal Wide Assurance is a statement made by the institution, which includes an appropriate

code, declaration or statement of ethical principles, along with a statement formulated by the institution itself.

2. The Carrick Institute has made a commitment to ensure that the IRB has sufficient clerical and other support including liability insurance for IRB members, so that the IRB may perform its required functions.

3. The Carrick Institute requires prompt reporting, in writing, by the investigator to the IRB, to the administrator, and to Dr. Carrick (if not serving as administrator) as well as the head of any US agency conducting or supporting the research if any of these events occur:

- a. Unanticipated problems involving risk to subjects or others
- b. Serious non-compliance of laws, regulations or IRB directions
- c. Suspension or termination of IRB approval

4. Written procedures for:

- a. Conducting the IRB's initial and continuing review (reviewing not less than once per year)
- b. Determining which projects will require review more than annually
- c. Ensuring prompt IRB update on any proposed changes to research activity

5. Upon request, provide copy of all of these written procedures to OHRP or any US federal department or agency conducting or supporting research to which the FWA applies.

6. The institution's FWA shall be completed and maintained by the IRB administrator. It must be renewed every 5 years. The institution must update the FWA within 90 days after changes of its legal Institution name, the Human Protections Administrator or the signatory official.

IV. Chain of authority and responsibilities:

II. Administrator:

The administrator serves as the primary contact for OHRP and other government agencies regarding human research protection issues for the

organization. The Director has responsibility for the organization's distributed program for protecting human participants in research.

III. Chair and Vice-Chair:

The Chair and Vice Chair are directly responsible for overseeing the protection of research participants by ensuring the proper review, approval, disapproval, expediting or determination of exemption from further review of research protocol submissions to the IRB.

Together they are also responsible for the continued development and implementation of a post-IRB approval-monitoring program of research studies involving human subjects, as well as other quality improvement activities.

IV. IRB Members:

The IRB members are charged with responsibility to review proposed research in order to ensure that the rights of research participants are protected and that risk of harm to participants is minimized.

B. Electronic Meetings:

Due to the cross-country location of various members as well as the need for documentation, meetings will be held in the IRB room of the Carrick Institute's Adobe Connect. Members are identified and noted as present by logging in for their attendance.

I. Frequency:

Meetings shall be held on a monthly basis or as needed to fulfill the requirements of the IRB's duty. The chair or vice chair may call a meeting between regularly scheduled meeting as necessary to address IRB concerns. Meeting days and times will be set so as to allow a quorum of members to attend.

II. Quorum:

A quorum consists of one more than half of all members (excluding the Administrator). Therefore if there are nine members including the Administrator on the IRB, a quorum to hold a meeting would be obtained by five members being present (9- Administrator = 8; $8/2=4$; $4+1=5$).

III. Voting:

While unanimous decisions are ideal and may be strived for, it is not necessary. Voting consists of a simple majority. So for a quorum of five members, “three votes to two” would be a simple majority.

Any member with a conflict of interest in the review of proposal will not be able to vote. Conflicts of interest may include: relationship with an investigator, financial link to the outcome of a study, or any other undue influence.

C. Communication:

Communication should be open and free through the various levels of the IRB. Members, vice chair, chair and administrators should have an open dialogue.

When possible and appropriate records of IRB business should be maintained via email print outs, PowerPoints of meeting agendas and Adobe Connect meeting recordings.

D. Internal Ensuring Compliance and Self Audits

To insure quality and to follow a process of continuous improvement regular audits of at least once per year will be performed by the chair and vice chair and/or other assigned member(s) to assure completeness and adherence to the Carrick Institute’s own rigorous standards along with adherence to appropriate federal and state laws. The following areas will be reviewed during this process:

I. Compliance:

1. Compliance will be maintained with the following regulating bodies and laws:
2. HIPPA
3. DHHS Regulations
4. FDA
5. OPRR
6. State Laws within USA or equivalent if international

II. Directed and Complete Documentation:

By using standardized documentation and forms; along with checking for completion before the reviewing process, efficiency as well as quality can be assured. Forms should be modified as necessary to address concerns as well as new knowledge or changes in requirements as is appropriate.

III. Regular Training:

Initial and regular training of IRB members is necessary for maintaining quality of the review process. NIH PHRP certificates are the standard minimum for all IRB members.

Additional training is recommended during meetings as time and need requires. For example, a new board with members who have not served on an IRB will require more training and perhaps more reinforcement than a board consisting of all chairpersons of other IRBs.

Chair and vice chair may require additional training to serve in their capacities. Training for this is available from organizations such as the Collaborative Institutional Training Initiative (CITI).

Further training for the entire IRB may be appropriate as the board evolves towards certification through organizations such as Association for the Accreditation of Human Research Protection Programs (AAHRPP) or Certified IRB Professional (CIP)

IV. Internal Audits:

Internal audits allow us to retrospectively evaluate our processes. It allows for corrections and is a method of confirming completion of the research in a timely manner; and if not completed, triggers a continued review. It is for this reason this must be done at least once per year.

V. Annual Review of Laws and Regulations:

1. Laws, regulations and guides may change over time. It is for this reason a minimum of an annual review should be performed to update this manual and the Institute's procedures and forms as appropriate.
2. Examples of questions that may be used for self-audit include:
3. Do institutional policies comply with applicable regulations and promote appropriate review and approval?
4. Are the relevant institutional channels of communication sufficiently open?
5. Do adequate procedures for monitoring research and conduction audits of the research process exist?
6. Does the institution adequately provide for the training of personnel in policies and procedures related to human research with human subjects?

7. Does the institution support educational activities related to design, conduct and approval of research?

E. External Audits:

It is the policy of this IRB and the Carrick Institute to comply with all federal and state laws, regulations and policies. For that reason, this IRB will comply and assist with any audit by proper authority as in a manner that is appropriate.

Chapter 4: The IRB Review Process

I. **Training for PI.** Before the IRB can approve the research protocol, the PI, all co-investigators, and all personnel named on the protocol must successfully complete the IRB online training addressing the appropriate conduct of human participant research. Proof of completion of this requirement by all investigators and key personnel is maintained in the protocol file. The training must be renewed at a minimum of every year. This training is available at this link: <https://phrp.nihtraining.com/users/login.php>

II. **Forms to be Completed and Submitted by PI (and how to submit them):**

1. All forms should be saved and submitted in Adobe PDF files so as to allow easy distribution to IRB members for their review.

Forms submitted include:

2. NIH PHRP Certificate (current within one year)
3. Application
4. Consent/Assent form(s)
5. External Funding proposal
6. Recruitment materials
7. All study instruments (questionnaires, surveys, contact letters, instructions for research assistants)

III. **Submission requirements and procedures for request for exemption from review**

(Initial review process to determine whether a research activity needs IRB Review)

If the statements below are true, then it should not be considered research (does not need a review by the IRB). The IRB chair and vice chair may consider the study to be exempt from IRB review. You should fill out the necessary forms and receive a designation of *Exempt Review*.

1. Research in normal educational setting involving normal educational practices
2. Research involving educational tests, interviews etc., unless the human subjects can be individually identified or disclosure of their responses put them at risk of an adverse event
3. Research involving educational tests, interviews etc., unless the human subjects can be individually identified unless the subjects are elected or appointed public officials or candidates for public office. (Example, interviewing a public official is ok.)

4. Research involving the collection or study of existing data, documents or records if these sources are publicly available or if the information is such that the subjects cannot be identified.
-

If the answer is yes to any of the questions below, then it should be considered research and the activity must be approved by the IRB before it begins.

1. Is it an activity designed to test a hypothesis, permit conclusions to be drawn?
 2. Does it permit conclusions to be drawn?
 3. Does it develop or contribute to generalizable knowledge (expressed, for example, in theories, principles and statements of relationships)?
 4. Does it permit conclusions to be drawn?
 5. Is the activity designed to test a hypothesis?
-

If a Principal Investigator (PI) determines that a research activity constitutes human participant research and requires IRB review and approval, the PI must complete and submit to the chair of the IRB the research protocol and all supporting documents required for IRB initial review and approval under one of two processes: Expedited Review or Full Committee Review.

Once approved and initiated, every research protocol is subject to Continuing Review. This means that every protocol must be submitted for review and continuation of IRB approval under the Expedited or Convened Committee process at an interval appropriate to the protocol's degree of risk, but not less than once per year. This Policy & Procedure sets forth the research protocol application submission requirements, criteria for IRB approval, and procedures for each review process.

IV. If the Principal Investigator (PI) determines that a research activity constitutes human participant research and is not eligible for exemption from IRB review, the PI must submit the research protocol for IRB review and approval under the Expedited Review or Full Committee Review process.

V. Procedure for Expedited Review

1. Only the Chair of the IRB, or an experienced IRB reviewer who has been designated by the Chair of the IRB may make the determination that a research protocol application is eligible for Expedited Review and approval. An IRB member with relevant expertise will be selected by the Chair of the IRB as the Expedited Reviewer for the protocol. The Expedited Reviewer will review the application and provide comments to the IRB chair; who will provide written documentation of the comments, questions, and/or suggestions for revisions to the PI, who will respond in writing back to the IRB chair.

2. The Expedited Reviewer or the Chair of the IRB will review the response by the PI. These communications may continue until the Expedited Reviewer or the Chair of the IRB approves the protocol or refers the protocol for review by the Convened IRB. An expedited reviewer may not disapprove a research protocol alone. If the concerns are whether or not a project meets the definition of minimal risk or if the project may involve procedures that cannot be reasonably reviewed by an expedited review process, the protocol will be submitted for consideration at a convened IRB meeting.

VI. The Review Process:

3. First round of review: an IRB member will confirm NIH PHRP certificate is current, review the application, consent form, and any related documents. For anything that needs clarification, or is incomplete, or clearly does not meet current standards and federal guidelines, the investigator will receive a request for revisions. A well-written and complete application may not need round 1. Projects that qualify as "expedited" or "exempt from full review" may not need rounds 2 or 3.

4. Second round of review: The revised materials get sent by e-mail to the other Institutional Review Board members, who will review your plan in terms of participant safety; how participants are likely to be affected ethically, emotionally, and psychologically; participant privacy and confidentiality issues; risks versus benefits; and the overall quality of design (e.g., a poorly designed project which would not produce useable data would not be approved.) We summarize our findings and send you a request for revisions and clarifications.

5. Third round: The IRB meets as a group to discuss the project; the PI and other investigators may be asked to attend the meeting in case we

want a face-to-face discussion. Ideally, major issues have already been worked through and the meeting ends with a vote.

- a. Minor Revisions: The Expedited Reviewer(s) or the IRB may stipulate that approval of the research protocol will be granted only after the PI makes specific minor revisions to the protocol, informed consent documents and/or process, recruitment materials, etc. The IRB will send the PI a notification of the required changes. If the PI makes the revisions, he or she shall then submit them for review via the Expedited Review process. After all specific minor revisions have been approved; the IRB will send a written notice of approval to the PI. Upon receipt of the notice, the PI may initiate the research activity.
- b. If, however, the PI suggests or makes revisions that the Expedited Reviewer believes affect the risk-benefit ratio of the project, such revisions will be designated as major and referred for review by the convened IRB.
- c. Tabled: A protocol is tabled when the Expedited Reviewer(s) or the Convened IRB request additional information, substantive clarifications or modifications regarding the protocol, informed consent documents, etc. that are relevant to the evaluation of the risk/benefit ratio required for approval.

6. The IRB may also table a protocol where it does not have a member with expertise adequate to the scope and complexity of the proposed research and thus seeks review by an expert in the appropriate field. The PI may suggest an expert to the IRB for this purpose. When a protocol is tabled, the IRB shall send the PI a memorandum setting forth the reasons for this action. The PI shall have up to approximately 90 days to respond to the concerns outlined in the memorandum and to make appropriate revisions to the documents in question.

1. Approved: If the protocol is approved, the IRB will provide written notice of approval to the PI. Only after receiving the email notice of approval may the PI initiate the research activity.
2. All approvals will have an ending date. No approvals will be made for more than one year at a time. If study is not completed, a continuing review must be requested by the investigator.
3. Selective Observation: For approved research, the IRB has the authority to elect to observe, or to charge a third party to observe, either the consent process or the execution of any portion of the project.

4. Disapproved: The IRB at a convened meeting may elect to disapprove a research protocol when it identifies significant concerns about potential risk to participants or a lack of scientific validity to support the proposed research activities. The IRB will draft and transmit to the PI a written statement of the reasons for the IRB's decision. The PI will have the opportunity to respond in person or in writing. The IRB at a convened meeting will review any written responses and make a decision about the appeal of the initial decision to disapprove the research protocol. As with all protocols, the PI may not initiate the corresponding research activity until the protocol has been approved by the IRB. The PI always has the right to submit a new protocol that addresses the concerns outlined during the initial review.

VII. Procedures for continuing review:

7. A previously approved research study, that was not eligible for expedited review, must undergo a continuing IRB review process either at intervals appropriate to the degree of risk that were determined in the initial IRB approval, or not less than once per year. The IRB approval for continuation of a study must be granted before the end of the current approval period to avoid lapse. This review must be performed at a convened IRB meeting. The PI must submit the proper documentation for continuing review no less than 30 days before the designated time limit. The IRB may appoint members of the IRB as primary reviewers to facilitate the continuing review process at a convened meeting.
8. Continuing review for an expedited project needs the approval of the Chair of the IRB, or an experienced IRB reviewer who has been designated by the Chair, who may make the determination that a research protocol application is eligible for continuation. The PI must submit the proper documentation for continuing review no less than 30 days before the designated time limit. Disapproval of an expedited research project at the time of continuing review can only occur after review by the IRB at a convened meeting, not by the expedited review process. All IRB members must be advised of research that has been approved under an expedited review

VIII. Consequences of failure to submit protocol for continuing review:

Consequences of failure to submit protocol for continuing review will result in a lapse in IRB approval. When continuing review of a research project does not occur prior to the end of the approval

period specified by the IRB, IRB approval expires automatically. In such circumstances, all research activities involving human subjects must stop after IRB approval has expired, unless it is determined by the IRB to be in the best interests of already enrolled subjects to continue participating in the research. Enrollment of new subjects cannot occur after the expiration of IRB approval. Continuing participation of already enrolled subjects in a research project during the period when IRB approval has lapsed may be appropriate, for example, when the research interventions hold out the prospect of direct benefit to the subjects or when withholding those interventions poses increased risk to the subjects.

IX. IRB has authority to suspend or terminate approval of research:

The IRB has the authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that is associated with unexpected serious harm to subjects. A suspension or termination of IRB approval of research may occur at any time during the period for which IRB approval had already been given.

X. Procedures for submitting an amendment for review

Investigators must seek IRB approval before making any changes to an approved research study. Changes to the study protocol may not be implemented until approved by the IRB. A change may be implemented before IRB approval when the change is necessary to eliminate immediate hazard to the subject in which case the IRB must then be notified at once.

XI. Procedures for foreseeable adverse event:

Investigators are responsible for preparation for any foreseeable injury and for notifying the IRB should an event occur. Procedures should be set to minimize the possibility and severity of an adverse event. Plans for minimizing the event, a description of the remedy as well as the associated costs tied to a foreseeable adverse event should be described in the IRB application, consent and assents.

XII. Procedures for unanticipated injury to research participant:

In the even of an unforeseeable adverse event, the investigator should address any immediate medical situation appropriately; and immediately notify the IRB Administrator, IRB Chair and IRB Vice Chair. An action

plan to address the unique event and make the participant whole will then be assembled with appropriate input from IRB members, medical, legal and others as needed or appropriate.

XIII. Procedures for violation of IRB permissions, inappropriate actions, violations upon review.

Violations by investigators of IRB permissions or other ethical violations are serious events and must be reported immediately to the IRB. The IRB board is required to investigate all alleged misconduct.

Misconduct such as unreported changes in protocols, misuse or nonuse of informed consents/assents or failure to submit a protocol can be generally handled within the IRB. If an investigator avoids the IRB and begins research or ignores IRB rulings, the IRB and the Carrick Institute will work to halt all research until remedial actions allow the study to be brought into order.

Should the investigator continue to ignore the IRB, the IRB will report to the OPRR where the fitness of the investigator to conduct human research will be addressed.

XIV. All initial and continuing reviews

Whether expedited or fully convened IRB will be conducted in accordance with the following considerations:

I. Risk/Benefit Analysis: Anticipated benefits must outweigh the risks to the participant.

1. HHS rules state that:

- a. Risks must be minimized
- b. Unavoidable risks are justified and necessary for sound scientific design
- c. Research studies are expected to make worthwhile progress towards important generalizable knowledge.

2. Risks the human research participant may be exposed to include: physical, psychological, social, legal or economic:

- a. Risks that may be physical include pain and injury or an impairment of one of our senses such as sight or hearing.
- b. Psychological risks can include emotional distress, anxiety, regret or sadness.

- c. Legal risks could place the participant at risk for criminal or civil litigation.
- d. Social risks include personal and outsider opinions of the participant that could be negative and thus affecting their reputation, social or political standing.
- e. Economic risks could be involved if the information obtained could affect an individual's job, insurance premium or other unforeseen cost.

3. Questions to consider for risk/benefit analysis include:

- a. Are both risks and anticipated benefits accurately identified, evaluated, and described?
- b. Are the risks greater than minimal risk? Has the IRB taken into account any special vulnerability among prospective subjects that might be relevant to evaluating the risk of participation?
- c. If the research involves the evaluation of a therapeutic procedure, have the risks and benefits of the research interventions been evaluated separately from those of the therapeutic interventions?
- d. Has due care been used to minimize risks and maximize the likelihood of benefits?
- e. Are there adequate provisions for a continuing reassessment of the balance between risks and benefits? Should there be a data and safety monitoring committee?

XV. Informed Consent/Assent:

2. Informed consent is required. In the case of a minor or cognitively impaired individual, an assent is required. Informed consent is a process and not just a written form. Methods can be used to increase a potential participants understanding of the consent via use of a consent form, oral presentations, educational brochures and video presentations.

2. Three fundamental aspects needed for informed consent include:

- a. Voluntariness
- b. The individual must consent freely without influence from others
- c. Comprehension:

The individual must have the capability to understand and make a decision based on the information provided. The investigators must disclose the following in a manner that is reasonable for the purposes of the person making the decision to do so based on the:

- The purpose of the study
- Any foreseeable risks
- Potential benefits to the participant and others
- Alternatives available to her participant beyond the research protocol
- What confidentiality the participant can expect
- What compensation is available should and injury occur due to the protocol
- Who does the participant contact for questions regarding the study, their rights and in case of injury
- Under what conditions are they agreeing to participate in the study; including their right to withdraw or refuse to participate without penalty

XVI. Incentives for Participation:

1. During the process of consent/assent the investigator(s) should inform the participant:
 - a. If there will be compensation for participating
 - b. Appropriate expectations of full or partial compensation if they withdraw from participation
 - c. How much compensation will there be for participation to compensate for inconveniences as well as discomfort arriving from the research

2. Investigators should avoid undue inducement, which includes:
 - a. Offers that may blind the participant to the risks they are considering
 - b. Offers that may cause participants to hide information that may disqualify them from participating in the research.

XVII. Selection of Subjects

Fair procedures and outcomes should be used to select participants and there must be fair distribution of benefits as well as burdens in populations that participate in research. Inclusion of women and minorities is a part of the NIH inclusion policy.

Questions recommended by the OHRP's Institutional Review Board Guidebook for IRB members to consider in regards to subject selection include:

1. *Will the burdens of participating in the research fall on those most likely to benefit from the research?*
2. *Will the solicitation of subjects avoid placing a disproportionate share of the burdens of research on any single group?*
3. *Does the nature of the research require or justify using the proposed subject population?*
4. *Are there any groups of people who might be more susceptible to the risks presented by the study and who therefore ought to be excluded from the research? Are the procedures for identifying such individuals adequate?*
5. *To the extent that benefits to the subjects are anticipated, are they distributed fairly? Do other groups of potential subjects have a greater need to receive any of the anticipated benefits?*
6. *To the extent that participation in the study is burdensome, are these burdens distributed fairly? Is the proposed subject population already so burdened that it would be unfair to ask them to accept an extra burden?*
7. *Will any special physiological, psychological, or social characteristics of the subject group pose special risks for them?*
8. *Would it be possible to conduct the study with other, less vulnerable subjects? What additional expense or inconvenience would that entail? Does the convenience of the researcher or possible improvement in the quality of the research justify the involvement of subjects who may either be susceptible to pressure or who are already burdened?*
9. *Has the selection process overprotected potential subjects who are considered vulnerable (e.g., children, cognitively impaired, economically or educationally disadvantaged persons, patients of researchers, seriously ill persons) so that they are denied opportunities to participate in research?*
10. *If the subjects are susceptible to pressures, are there mechanisms that might be used to reduce the pressures or minimize their impact?*
11. Special classes will require considerations
Please see chapter 5 for more detail

XVIII. Privacy and Confidentiality

Investigators are responsible to maintain protections from unsanctioned intrusion and holding secret all information relating to an individual unless they give consent that permits disclosure. This may require properly disposing data and other records be they

electronic or paper as well as limiting access to these records by secured databases or otherwise locked access.

Questions the IRB should consider under the category of confidentiality per OHRP include:

1. *Does the research involve observation or intrusion in situations where the subjects have a reasonable expectation of privacy? Would reasonable people be offended by such an intrusion? Can the research be redesigned to avoid the intrusion?*
2. *If privacy is to be invaded, does the importance of the research objective justify the intrusion? What if anything, will the subject be told later?*
3. *If the investigators want to review existing records to select subjects for further study, whose permission should be sought for access to those records (the physician, the institution maintaining the records, the subjects)? How should the subjects be approached (through their physician, the medical records department, the institution)?*
4. *Will the investigator(s) be collecting sensitive information about individuals? If so, have they made adequate provisions for protecting the confidentiality of the data through coding, destruction of identifying information, limiting access to the data, or whatever methods that may be appropriate to the study? If the information obtained about subjects might interest law enforcement or other government agencies to the extent that they might demand personally identifiable information, can a grant of confidentiality be sought from a federal or state agency to protect the research data and the identity of the subjects from subpoena or other legal process?*
5. *Are the investigator's disclosures to subjects about confidentiality adequate? Should documentation of consent be waived in order to protect confidentiality?*

II. Decision on need for observation: For approved research, the IRB has the authority to elect to observe, or to charge a third party to observe, either the consent process or the execution of any portion of the project.

The OHRP Institutional Review Guidebook suggests the need for observation can be established by answering these questions:

1. *How will the research data be recorded and maintained?*

2. *Considering the degree of risk, is the plan for monitoring the research adequate in terms of timeliness and thoroughness?*
3. *If the principal investigator is other than full-time on the project, is the oversight and monitoring time sufficient?*
4. *Is there a mechanism for providing information to the IRB in the event that unexpected results are discovered? (Unexpected results may raise the possibility of unanticipated risks to subjects.)*
5. *Does the institution have a data and safety monitoring board? If so, should it be asked to monitor the project under review? If the institution does not have a data and safety monitoring board, should the IRB request or recommend that one be appointed, either by the institution or the sponsor, for this project?*

III. Additional Safeguards:

Additional safeguards to consider per OHRP guides may include:

1. *Are recruitment procedures designed to assure that informed consent is freely given?*
2. *What special safeguards are included to protect the rights and welfare of subjects who are likely to be vulnerable to coercion or undue influence (e.g., children, prisoners, pregnant women, persons with physical or mental illness, and persons who are economically or educationally disadvantaged)?*
3. *Does the nature of the disease or behavioral issue to be studied permit free consent?*
4. *Are any incentives offered for participation likely to unduly influence a prospective subject's decision to participate?*
5. *Is there an adequate procedure for monitoring the consent process, and should the IRB or its representative observe the process?*

IV. Continuing Review:

The determination for the need for continuing the review as the study goes on can be determined per OHRP guides by the following questions:

1. *Are the actual risks and benefits as anticipated? Have any subjects been seriously harmed? Has the IRB been informed of any unforeseen problems or accidents that may have occurred?*
2. *Should the IRB request that the investigator(s) submit scheduled progress reports? Should the investigator(s) submit progress reports more often than annually?*
3. *Since the last IRB review, have subjects been informed of any important new information that might affect their willingness to continue participating in the research?*

4. *Have any new findings, knowledge, or adverse effects come to light that should be, but have not been, communicated to subjects?*
5. *Does the progress of the project together with the results of other new research indicate that the IRB should either impose special precautions or relax special requirements it had previously imposed?*
6. *Do the consent documents need to be revised?*
7. *Has due care been used to reduce risks and increase the likelihood of benefit?*
8. *Are the procedures agreed upon at the beginning of the research still being used?*
9. *Does the protocol adequately provide for continuing assessment of the balance between risks and benefits?*
10. *When should the IRB next review the project (taking into account what has been learned about the actual risk to subjects since the project first received IRB approval)?*
11. *Should IRB approval be continued, or should approval be suspended or terminated?*

Chapter 5: Consideration of Special Classes of Subjects

Certain classes of research participants are classified as special, requiring additional consideration and review by the IRB. Examples include women, children & minors, cognitive impaired persons, prisoners, traumatized & comatose patients, terminally ill patients, elderly or aged persons and minorities.

Questions suggested by OHRP for the IRB to consider by group include:

A. Women:

- 1. For all studies, is there reason to exclude pregnant or lactating women? If so, how strict should the screening measures be?*
- 2. For all studies involving pregnant women, have appropriate studies on animals and non-pregnant humans been conducted? Is any special monitoring of the informed consent process needed?*
- 3. For studies directed toward maternal health, is the risk to the fetus the least possible consistent with the research objectives? Will the mother be adequately informed of the potential risk to the fetus and of alternative treatments and their risks and benefits?*
- 4. For studies of pregnancy, labor, or delivery, is the risk to the fetus "minimal?" Is the father's consent required?*
- 5. For studies of lactating women, is the supply and content of breast milk adequately protected?*
- 6. For studies of conception or contraception, are the risks, benefits, reversibility, and alternatives adequately explained? In contraceptive studies, is there adequate explanation of possible failure and of the options available for dealing with unintended pregnancies?*
- 7. Will women be appropriately represented in the study? Does the study need to be designed to allow evaluation of gender differences?*

B. Children & Minors:

- 1. Does the research have an identifiable prospect of direct benefit to the individual child participant?*
- 2. Can that benefit be achieved through alternative means?*
- 3. Does the research have an identifiable prospect of risk to the individual child participant? What safeguards are proposed to minimize these risks? When procedures involving greater than minimal risk to children are anticipated, are convincing scientific and ethical justifications given?*

4. *Is the inclusion of normal volunteers justified?*
5. *Do studies involving placebo controls place the child at greater risk by withholding from selected subjects potentially therapeutic research drugs or interventions?*
6. *When possible, have appropriate studies been conducted on animals and adults first? Will older children be enrolled before younger ones?*
7. *What is the age of majority in the state? Can a child consent to medical care for certain conditions, and, if so, at what age? What legal limits are there on the right of parents to consent on behalf of their children?*
8. *Is permission of both parents necessary? Under what conditions one of the parents may be considered "not reasonably available?"*
9. *Will efforts be made to ensure that parents' permission to involve their children in research studies is free from coercion, exploitation, and/or unrealistic promises?*
10. *Are mechanisms in place to ensure that children are involved as research subjects in ways that do not undermine their dignity as young persons? Are provisions made that show respect for the developing rights of children, such as: (a) obtaining their assent, and, where appropriate, honoring their dissent; and (b) protecting their need for privacy and the confidentiality of information regarding them?*
11. *Are there special problems that call for the presence of a monitor or advocate during consent procedures?*
12. *Are special needs of adolescents such as counseling and confidentiality accounted for in the research design?*
13. *Are there any special problems such as confidentiality and reporting that might arise in sensitive research about child abuse or sexual practices of teenagers?*
14. *If conditions present in children have implications for other family members' health statuses, are appropriate mechanisms proposed for dealing with the larger family unit (e.g., genetic risks or HIV infection)?*
15. *Should parents be required to be present during the conduct of the research? (Are proposed subjects to be very young? Are the procedures involved painful? Must subjects stay overnight in the hospital when they otherwise would not have to?)*

Chapter 6: Considerations of Research Design

IRB members are not required to review research design for its quality other than does the risk/benefit ratio of the study meet the requirements. The IRB does have a responsibility to make sure that the risks are reduced for the research participant.

1. Questions to consider related to reducing risks within the research design may include:

- Is the scientific design adequate to answer the questions posed?*
- 2. Is the sample size (number of subjects) adequate?*
- 3. Is the method proposed for selecting and assigning subjects to treatment groups unbiased?*
- 4. Does the investigator serve a dual role that may pose a conflict of interest?*
- 5. Is any of the information to be collected sensitive (e.g., related to sexual practices, substance abuse, or illegal behavior)?*
- 6. Are there adequate plans to protect participants from the risks of breach of confidentiality and invasion of privacy?*
- 7. Are there plans for approaching subjects in a way that will respect their privacy and their right to refuse?*
- 8. If the protocol involves an epidemiologic study, will subjects or their relatives be protected from learning inappropriate information?*
- 9. Does the recruitment process protect subjects from being coerced or unduly influenced to participate?*
- 10. Are any payments to subjects reasonable in relation to the risks, discomfort, or inconvenience to which subjects will be exposed?*
- 11. Are there adequate plans to exclude subjects who are vulnerable to injury during the period of withdrawal of active and effective therapy, if that is part of the research design?*
- 12. Have the rights and interests of vulnerable subjects (e.g., desperately ill persons) been adequately considered?*

Are all appropriate elements of informed consent clearly provided, including:

- 1. Do the consent documents describe the study design (including plans for randomization, use of placebos, and the probability that the subject will receive a given treatment) and conditions for breaking the code (if the study is masked)?*
- 2. Do the consent documents describe the risks and benefits of each of the proposed interventions and of alternative courses or actions available to the participants?*

3. Do the consent documents clearly describe the extent to which participation in the study precludes other therapeutic interventions?
4. Are provisions made for supplying new information to subjects during the course of the study and for obtaining continuing consent, where appropriate?
5. Must investigators obtain consent before reviewing records?
6. Will the consent process take place under conditions most likely to provide potential subjects an opportunity to make a decision about participation without undue pressure?
7. If the study is a clinical trial, how will the trial be monitored? What will be done with preliminary data? Should an independent data and safety monitoring board be established? How will decisions about stopping the trial be made? By whom? On what basis?
8. At what interval should the IRB perform continuing review of this project?

Chapter 7: Medical Device Research Issues

Anytime a device is used in the process of human research, then consideration of its use in terms of safety for the participant should be considered. IRB's should consider three basic questions in consideration when medical devices are a part of the research process.

- A. What risks are presented by the use of the device? Are they significant or non-significant?
- B. Have other IRBs reviewed and made decisions regarding this device? (Such information should be available from the sponsor or clinical investigator.)
- C. What is the status of the device with the FDA? Has the device been approved for marketing? Is the device approved for other indications? Is it now being studied for a different indication? Is an IDE needed for this device? If so, has it been approved?

Chapter 8: Glossary of Terms

Clinical trial - A prospective biomedical or behavioral research study of human subjects that is designed to answer specific questions about biomedical interventions. Clinical trials are used to determine whether new biomedical or behavioral interventions are safe, efficacious and effective

Coercion - An overt or implicit threat of harm that is intentionally presented by one person to another in order to obtain agreement.

Confidentiality - pertains to the treatment of information (data) that an individual has disclosed in a relationship of trust and with the expectation that it will not be divulged to others without permission in way that are inconsistent with the understanding of the original disclosure.

Deception - The intentional misleading of subjects or the withholding of full information about the nature of the experiment.

Decisionally Impaired Adult - An individual who has a diminished capacity for judgment and reasoning due to a psychiatric, organic, developmental, or other disorder that affects cognitive or emotional functions. Individuals who are decisionally impaired may suffer from many different conditions that could potentially affect their ability to reason and make sound choices. The level of impairment may fluctuate or progressively change over time. An individual's capacity may also be specific to the particular task, point-in-time, or decision-making circumstance. Examples of decisionally impaired individuals include those impaired by a stroke, traumatic brain injury, Alzheimer's disease, individuals under the influence of or dependent on drugs or alcohol, terminally ill patients, and mental illness such as schizophrenia, depression, or Post-Traumatic Stress Disorder. Other individuals, who may be considered decisionally impaired with limited decision-making ability, include individuals who have lost cognitive ability due to trauma, anesthetics, analgesics, or extreme pain, such as in an emergency room setting or preparatory to surgery.

Emancipated Minor - "Emancipated" means that the rights of the parents to the custody, control, services, and earnings of a minor have been terminated. "Minor" means a person who is at least 16 but less than 18

years of age. Emancipation may occur by operation of law (when a minor is validly married or reaches 18 or during the period when the minor is on active duty within the US armed forces) or pursuant to a petition filed by a minor with the juvenile court. Emancipated minors may consent to research participation for themselves.

Generalizable Knowledge - Data gathered with the intent to draw conclusions from the research which will develop or contribute to a general body of knowledge.

Human Subject (As Defined by DHHS) - a living individual about whom an investigator conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information.

Identifiable information - information that is individually identifiable (for example the identity of the subject is or may readily be ascertained by the investigator or associated with the information).

Incapacity - a person's mental status and an inability to understand information presented, to appreciate the consequences of acting (or not acting) on that information, and to make a choice. Often used as a synonym for incompetence.

Incompetence - Technically, a legal term meaning inability to manage one's own affairs. Often used as a synonym for incapacity.

Informed Consent - a person's voluntary agreement, based upon adequate knowledge and understanding of relevant information, to participate in research or to under diagnostic, therapeutic, or preventive procedure.

Institutional Review Board - Any board, committee or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of research involving human subjects.

Interaction - communication or interpersonal contact between the investigator and the subject.

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

Investigator - An individual who conducts and directs the study, carries the ultimate responsibility for the research, and is referred to as the Principal Investigator. The institution recognizes a single

individual to serve as the Principal Investigator of human subject research.

Minimal Risk - The probability and magnitude of harm or discomfort anticipated in the research are not greater than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

Minimal Risk for Prisoners - The probability and magnitude of physical or psychological harm that is normally encountered in the daily lives or in the routine medical, dental, or psychological examination of a healthy person.

Modifications that are Minor - Minor modifications are changes that can be easily ascertained that they have been completed. They generally do not affect the criteria listed in 45 CFR 46.111.

Non-Compliance - Any action or activity associated with the conduct or oversight of research involving human subjects that fails to comply with either the research plan as approved by a designated Institutional Review Board, or federal regulations or institutional policies governing such research. Noncompliance may range from minor to serious, be unintentional or willful, and may occur once or several times.

Privacy - The control over the extent, timing, and circumstances of sharing oneself (physically, behaviorally, or intellectually) with others.

Private information - information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record).

Prospective Studies - Studies that gather information about events that occur after the identification of the group of subjects to be studied. Prospective studies may involve intervention or may be solely observations or may involve only the collection of data.

Protocol - The plan of a study. The protocol should include the study title; a summary; a description that includes a rationale, objectives, methodology, and data management and analysis; ethical consideration, and references.

Protocol Deviation - A deviation from Institutional Review Board-approved activities related to a research study. This means that the principal investigator(s) has performed activities that are different than those described in the protocol, that procedures not previously described in the protocol were performed, or that procedures described in the protocol were not performed.

Quorum - A majority of the voting members. In the instance of the Institutional Review Board (IRB), a quorum will consist of greater than 50% of the voting IRB members and must include at least one non-scientific member. All members present have equal voting power. At meeting of the IRB, a quorum must be established and maintained throughout the entire meeting. A member with a conflict of interest cannot contribute to a quorum.

Research (DHHS) - A systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.

Risk - The probably of harm or injury (physical, psychological, social, economic) occurring as a result of participation in a research study.

Serious Non-Compliance - Failure to adhere to the terms of the IRB approval and/or abide by the applicable laws, regulations or institutional policies when that failure increases risks to subjects or others or adversely affect the rights and welfare of the subjects. Willful violation of policies and/or federal regulations may also constitute serious non-compliance. Serious non-compliance is a finding that is determined by the convened board.

Sponsor - Any person or entity that takes the responsibility for funding a study. The sponsor may be an individual, governmental agency, academic institution, private or other organization.

Suspension - An action by the convened IRB, an IRB Chair/Vice Chair or the IO or his designee to stop, temporarily or permanently, some or all previously approved research activities short of permanently stopping all research activities. Suspended protocols are not closed with the IRB and require continuing review by the IRB.

Systematic Investigation - An approach to seeking knowledge involving a predetermined method for studying a specific topic, answering a specific question, testing a specific hypothesis, or developing a theory.

Termination - A termination is an action by the convened IRB to stop permanently all activities of a previously approved research protocol. Terminated protocols are closed protocols, and they no longer require continuing review.

Unanticipated Event/Unanticipated Problem Involving Risk to Subjects or Others - Any problem, event, occurrence or new information related to the research project that is unanticipated and indicates subjects or others are at increased risk of harm. An unanticipated event or problem is one that is unforeseen in terms of nature, severity or frequency of occurrence as documented in the research or other materials approved by the IRB.

Voluntary - Free of coercion, duress, or undue inducement. Used in the research context to refer to a subject's decision to participate (or to continue to participate) in a research activity.

Chapter 9 Appendix

I. Nuremberg Code

1. The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved, as to enable him to make an understanding and enlightened decision. This latter element requires that, before the acceptance of an affirmative decision by the experimental subject, there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person, which may possibly come from his participation in the experiment.

The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.

3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study, that the anticipated results will justify the performance of the experiment.

4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.

5. No experiment should be conducted, where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.

6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

7. Proper preparations should be made and adequate facilities provided

to protect the experimental subject against even remote possibilities of injury, disability, or death.

8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.

9. During the course of the experiment, the human subject should be at liberty to bring the experiment to an end, if he has reached the physical or mental state, where continuation of the experiment seemed to him to be impossible.

10. During the course of the experiment, the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him, that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

["Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10", Vol. 2, pp. 181-182. Washington, D.C.: U.S. Government Printing Office, 1949.]

Retrieved on 6/25/14 from:
<http://history.nih.gov/research/downloads/nuremberg.pdf>

II. Declaration of Helsinki

Preamble

The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

Medical progress is based on research that ultimately must include studies involving human subjects.

The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

Medical research should be conducted in a manner that minimizes possible harm to the environment.

Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimize the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm. All vulnerable groups and individuals should receive specifically considered protection.

Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee

before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorized representative.

The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention. Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

Retrieved from: <http://www.wma.net/en/30publications/10policies/b3/> on 6/25/14.

III. Belmont Report

Ethical Principles & Guidelines for Research Involving Human Subjects

Scientific research has produced substantial social benefits. It has also posed some troubling ethical questions. Public attention was drawn to these questions by reported abuses of human subjects in biomedical experiments, especially during the Second World War. During the Nuremberg War Crime Trials, the Nuremberg code was drafted as a set of standards for judging physicians and scientists who had conducted biomedical experiments on concentration camp prisoners. This code became the prototype of many later codes (1) intended to assure

that research involving human subjects would be carried out in an ethical manner.

The codes consist of rules, some general, others specific that guide the investigators or the reviewers of research in their work. Such rules often are inadequate to cover complex situations; at times they come into conflict, and they are frequently difficult to interpret or apply. Broader ethical principles will provide a basis on which specific rules may be formulated, criticized and interpreted.

Three principles, or general prescriptive judgments, that are relevant to research involving human subjects are identified in this statement. Other principles may also be relevant. These three are comprehensive, however, and are stated at a level of generalization that should assist scientists, subjects, reviewers and interested citizens to understand the ethical issues inherent in research involving human subjects. These principles cannot always be applied so as to resolve beyond dispute particular ethical problems. The objective is to provide an analytical framework that will guide the resolution of ethical problems arising from research involving human subjects.

This statement consists of a distinction between research and practice, a discussion of the three basic ethical principles, and remarks about the application of these principles.

Part A: Boundaries Between Practice & Research

A. Boundaries Between Practice and Research

It is important to distinguish between biomedical and behavioral research, on the one hand, and the practice of accepted therapy on the other, in order to know what activities ought to undergo review for the protection of human subjects of research. The distinction between research and practice is blurred partly because both often occur together (as in research designed to evaluate a therapy) and partly because notable departures from standard practice are often called "experimental" when the terms "experimental" and "research" are not carefully defined.

For the most part, the term "practice" refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment or therapy to particular individuals. (2) By contrast, the term "research" designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories,

principles, and statements of relationships). Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective.

When a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research. The fact that a procedure is "experimental," in the sense of new, untested or different, does not automatically place it in the category of research. Radically new procedures of this description should, however, be made the object of formal research at an early stage in order to determine whether they are safe and effective. Thus, it is the responsibility of medical practice committees, for example, to insist that a major innovation be incorporated into a formal research project. (3)

Research and practice may be carried on together when research is designed to evaluate the safety and efficacy of a therapy. This need not cause any confusion regarding whether or not the activity requires review; the general rule is that if there is any element of research in an activity, that activity should undergo review for the protection of human subjects.

Part B: Basic Ethical Principles

B. Basic Ethical Principles

The expression "basic ethical principles" refers to those general judgments that serve as a basic justification for the many particular ethical prescriptions and evaluations of human actions. Three basic principles, among those generally accepted in our cultural tradition, are particularly relevant to the ethics of research involving human subjects: the principles of respect of persons, beneficence and justice.

1. **Respect for Persons.** -- Respect for persons incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. The principle of respect for persons thus divides into two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy.

An autonomous person is an individual capable of deliberation about personal goals and of acting under the direction of such deliberation. To respect autonomy is to give weight to autonomous persons' considered opinions and choices while refraining from obstructing their actions unless they are clearly detrimental to others. To show lack of respect for an autonomous agent is to repudiate that person's considered judgments, to deny an individual the freedom to act on those considered judgments, or to withhold information necessary to make a considered judgment, when there are no compelling reasons to do so.

However, not every human being is capable of self-determination. The capacity for self-determination matures during an individual's life, and some individuals lose this capacity wholly or in part because of illness, mental disability, or circumstances that severely restrict

liberty. Respect for the immature and the incapacitated may require protecting them as they mature or while they are incapacitated.

Some persons are in need of extensive protection, even to the point of excluding them from activities which may harm them; other persons require little protection beyond making sure they undertake activities freely and with awareness of possible adverse consequence. The extent of protection afforded should depend upon the risk of harm and the likelihood of benefit. The judgment that any individual lacks autonomy should be periodically reevaluated and will vary in different situations.

In most cases of research involving human subjects, respect for persons demands that subjects enter into the research voluntarily and with adequate information. In some situations, however, application of the principle is not obvious. The involvement of prisoners as subjects of research provides an instructive example. On the one hand, it would seem that the principle of respect for persons requires that prisoners not be deprived of the opportunity to volunteer for research. On the other hand, under prison conditions they may be subtly coerced or unduly influenced to engage in research activities for which they would not otherwise volunteer. Respect for persons would then dictate that prisoners be protected. Whether to allow prisoners to "volunteer" or to "protect" them presents a dilemma. Respecting persons, in most hard cases, is often a matter of balancing competing claims urged by the principle of respect itself.

2. Beneficence. -- Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being. Such treatment falls under the principle of beneficence. The term "beneficence" is often understood to cover acts of kindness or charity that go beyond strict obligation. In this document, beneficence is understood in a stronger sense, as an obligation. Two general rules have been formulated as complementary expressions of beneficent actions in this sense: **(1)** do not harm and **(2)** maximize possible benefits and minimize possible harms.

The Hippocratic maxim "do no harm" has long been a fundamental principle of medical ethics. Claude Bernard extended it to the realm of research, saying that one should not injure one person regardless of the benefits that might come to others. However, even avoiding harm requires learning what is harmful; and, in the process of obtaining this information, persons may be exposed to risk of harm. Further, the Hippocratic Oath requires physicians to benefit their patients "according to their best judgment." Learning what will in fact benefit may require exposing persons to risk. The problem posed by these imperatives is to decide when it is justifiable to seek certain benefits despite the risks involved, and when the benefits should be foregone because of the risks.

The obligations of beneficence affect both individual investigators and society at large, because they extend both to particular research projects and to the entire enterprise of research. In the case of particular projects, investigators and members of their institutions

are obliged to give forethought to the maximization of benefits and the reduction of risk that might occur from the research investigation. In the case of scientific research in general, members of the larger society are obliged to recognize the longer term benefits and risks that may result from the improvement of knowledge and from the development of novel medical, psychotherapeutic, and social procedures.

The principle of beneficence often occupies a well-defined justifying role in many areas of research involving human subjects. An example is found in research involving children. Effective ways of treating childhood diseases and fostering healthy development are benefits that serve to justify research involving children -- even when individual research subjects are not direct beneficiaries. Research also makes it possible to avoid the harm that may result from the application of previously accepted routine practices that on closer investigation turn out to be dangerous. But the role of the principle of beneficence is not always so unambiguous. A difficult ethical problem remains, for example, about research that presents more than minimal risk without immediate prospect of direct benefit to the children involved. Some have argued that such research is inadmissible, while others have pointed out that this limit would rule out much research promising great benefit to children in the future. Here again, as with all hard cases, the different claims covered by the principle of beneficence may come into conflict and force difficult choices.

3. Justice. -- Who ought to receive the benefits of research and bear its burdens? This is a question of justice, in the sense of "fairness in distribution" or "what is deserved." An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly. Another way of conceiving the principle of justice is that equals ought to be treated equally. However, this statement requires explication. Who is equal and who is unequal? What considerations justify departure from equal distribution? Almost all commentators allow that distinctions based on experience, age, deprivation, competence, merit and position do sometimes constitute criteria justifying differential treatment for certain purposes. It is necessary, then, to explain in what respects people should be treated equally. There are several widely accepted formulations of just ways to distribute burdens and benefits. Each formulation mentions some relevant property on the basis of which burdens and benefits should be distributed. These formulations are **(1)** to each person an equal share, **(2)** to each person according to individual need, **(3)** to each person according to individual effort, **(4)** to each person according to societal contribution, and **(5)** to each person according to merit.

Questions of justice have long been associated with social practices such as punishment, taxation and political representation. Until recently these questions have not generally been associated with scientific research. However, they are foreshadowed even in the earliest reflections on the ethics of research involving human subjects. For example, during the 19th and early 20th centuries the burdens of serving as research subjects fell largely upon poor ward patients, while the benefits of improved medical care flowed primarily to private

patients. Subsequently, the exploitation of unwilling prisoners as research subjects in Nazi concentration camps was condemned as a particularly flagrant injustice. In this country, in the 1940's, the Tuskegee syphilis study used disadvantaged, rural black men to study the untreated course of a disease that is by no means confined to that population. These subjects were deprived of demonstrably effective treatment in order not to interrupt the project, long after such treatment became generally available.

Against this historical background, it can be seen how conceptions of justice are relevant to research involving human subjects. For example, the selection of research subjects needs to be scrutinized in order to determine whether some classes (e.g., welfare patients, particular racial and ethnic minorities, or persons confined to institutions) are being systematically selected simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied. Finally, whenever research supported by public funds leads to the development of therapeutic devices and procedures, justice demands both that these not provide advantages only to those who can afford them and that such research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research.

Part C: Applications

C. Applications

Applications of the general principles to the conduct of research leads to consideration of the following requirements: informed consent, risk/benefit assessment, and the selection of subjects of research.

1. Informed Consent. -- Respect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them. This opportunity is provided when adequate standards for informed consent are satisfied.

While the importance of informed consent is unquestioned, controversy prevails over the nature and possibility of an informed consent. Nonetheless, there is widespread agreement that the consent process can be analyzed as containing three elements: information, comprehension and voluntariness.

Information. Most codes of research establish specific items for disclosure intended to assure that subjects are given sufficient information. These items generally include: the research

procedure, their purposes, risks and anticipated benefits, alternative procedures (where therapy is involved), and a statement offering the subject the opportunity to ask questions and to withdraw at any time from the research. Additional items have been proposed, including how subjects are selected, the person responsible for the research, etc.

However, a simple listing of items does not answer the question of what the standard should be for judging how much and what sort of information should be provided. One standard frequently invoked in medical practice, namely the information commonly provided by practitioners in the field or in the locale, is inadequate since research takes place precisely when a common understanding does not exist. Another standard, currently popular in malpractice law, requires the practitioner to reveal the information that reasonable persons would wish to know in order to make a decision regarding their care. This, too, seems insufficient since the research subject, being in essence a volunteer, may wish to know considerably more about risks gratuitously undertaken than do patients who deliver themselves into the hand of a clinician for needed care. It may be that a standard of "the reasonable volunteer" should be proposed: the extent and nature of information should be such that persons, knowing that the procedure is neither necessary for their care nor perhaps fully understood, can decide whether they wish to participate in the furthering of knowledge. Even when some direct benefit to them is anticipated, the subjects should understand clearly the range of risk and the voluntary nature of participation.

A special problem of consent arises where informing subjects of some pertinent aspect of the research is likely to impair the validity of the research. In many cases, it is sufficient to indicate to subjects that they are being invited to participate in research of which some features will not be revealed until the research is concluded. In all cases of research involving incomplete disclosure, such research is justified only if it is clear that **(1)** incomplete disclosure is truly necessary to accomplish the goals of the research, **(2)** there are no undisclosed risks to subjects that are more than minimal, and **(3)** there is an adequate plan for debriefing subjects, when appropriate, and for dissemination of research results to them. Information about risks should never be withheld for the purpose of eliciting the cooperation of subjects, and truthful answers should always be given to direct questions about the research. Care should be taken to distinguish cases in which disclosure would destroy or invalidate the research from cases in which disclosure would simply inconvenience the investigator.

Comprehension. The manner and context in which information is conveyed is as important as the information itself. For example, presenting information in a disorganized and rapid fashion, allowing too little time for consideration or curtailing opportunities for questioning, all may adversely affect a subject's ability to make an informed choice.

Because the subject's ability to understand is a function of intelligence, rationality, maturity and language, it is necessary to adapt the presentation of the information to the subject's capacities. Investigators are responsible for ascertaining that the subject has comprehended the information. While there is always an obligation to ascertain that the information about risk to subjects is complete and adequately comprehended, when the risks are more serious, that obligation increases. On occasion, it may be suitable to give some oral or written tests of comprehension.

Special provision may need to be made when comprehension is severely limited -- for example, by conditions of immaturity or mental disability. Each class of subjects that one might consider as incompetent (e.g., infants and young children, mentally disable patients, the terminally ill and the comatose) should be considered on its own terms. Even for these persons, however, respect requires giving them the opportunity to choose to the extent they are able, whether or not to participate in research. The objections of these subjects to involvement should be honored, unless the research entails providing them a therapy unavailable elsewhere. Respect for persons also requires seeking the permission of other parties in order to protect the subjects from harm. Such persons are thus respected both by acknowledging their own wishes and by the use of third parties to protect them from harm.

The third parties chosen should be those who are most likely to understand the incompetent subject's situation and to act in that person's best interest. The person authorized to act on behalf of the subject should be given an opportunity to observe the research as it proceeds in order to be able to withdraw the subject from the research, if such action appears in the subject's best interest.

Voluntariness. An agreement to participate in research constitutes a valid consent only if voluntarily given. This element of informed consent requires conditions free of coercion and undue influence. Coercion occurs when an overt threat of harm is intentionally presented by one person to another in order to obtain compliance. Undue influence, by contrast, occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance. Also, inducements that would ordinarily be acceptable may become undue influences if the subject is especially vulnerable.

Unjustifiable pressures usually occur when persons in positions of authority or commanding influence -- especially where possible sanctions are involved -- urge a course of action for a

subject. A continuum of such influencing factors exists, however, and it is impossible to state precisely where justifiable persuasion ends and undue influence begins. But undue influence would include actions such as manipulating a person's choice through the controlling influence of a close relative and threatening to withdraw health services to which an individual would otherwise be entitled.

2. Assessment of Risks and Benefits. -- The assessment of risks and benefits requires a careful array of relevant data, including, in some cases, alternative ways of obtaining the benefits sought in the research. Thus, the assessment presents both an opportunity and a responsibility to gather systematic and comprehensive information about proposed research. For the investigator, it is a means to examine whether the proposed research is properly designed. For a review committee, it is a method for determining whether the risks that will be presented to subjects are justified. For prospective subjects, the assessment will assist the determination whether or not to participate.

The Nature and Scope of Risks and Benefits. The requirement that research be justified on the basis of a favorable risk/benefit assessment bears a close relation to the principle of beneficence, just as the moral requirement that informed consent be obtained is derived primarily from the principle of respect for persons. The term "risk" refers to a possibility that harm may occur. However, when expressions such as "small risk" or "high risk" are used, they usually refer (often ambiguously) both to the chance (probability) of experiencing a harm and the severity (magnitude) of the envisioned harm.

The term "benefit" is used in the research context to refer to something of positive value related to health or welfare. Unlike, "risk," "benefit" is not a term that expresses probabilities. Risk is properly contrasted to probability of benefits, and benefits are properly contrasted with harms rather than risks of harm. Accordingly, so-called risk/benefit assessments are concerned with the probabilities and magnitudes of possible harm and anticipated benefits. Many kinds of possible harms and benefits need to be taken into account. There are, for example, risks of psychological harm, physical harm, legal harm, social harm and economic harm and the corresponding benefits. While the most likely types of harms to research subjects are those of psychological or physical pain or injury, other possible kinds should not be overlooked.

Risks and benefits of research may affect the individual subjects, the families of the individual subjects, and society at large (or special groups of subjects in society). Previous codes and Federal regulations have required that risks to subjects be outweighed by the sum of both the anticipated benefit to the subject, if any, and the anticipated benefit to society in the form of

knowledge to be gained from the research. In balancing these different elements, the risks and benefits affecting the immediate research subject will normally carry special weight. On the other hand, interests other than those of the subject may on some occasions be sufficient by themselves to justify the risks involved in the research, so long as the subjects' rights have been protected. Beneficence thus requires that we protect against risk of harm to subjects and also that we be concerned about the loss of the substantial benefits that might be gained from research.

The Systematic Assessment of Risks and Benefits. It is commonly said that benefits and risks must be "balanced" and shown to be "in a favorable ratio." The metaphorical character of these terms draws attention to the difficulty of making precise judgments. Only on rare occasions will quantitative techniques be available for the scrutiny of research protocols. However, the idea of systematic, non-arbitrary analysis of risks and benefits should be emulated insofar as possible. This ideal requires those making decisions about the justifiability of research to be thorough in the accumulation and assessment of information about all aspects of the research, and to consider alternatives systematically. This procedure renders the assessment of research more rigorous and precise, while making communication between review board members and investigators less subject to misinterpretation, misinformation and conflicting judgments. Thus, there should first be a determination of the validity of the presuppositions of the research; then the nature, probability and magnitude of risk should be distinguished with as much clarity as possible. The method of ascertaining risks should be explicit, especially where there is no alternative to the use of such vague categories as small or slight risk. It should also be determined whether an investigator's estimates of the probability of harm or benefits are reasonable, as judged by known facts or other available studies.

Finally, assessment of the justifiability of research should reflect at least the following considerations: **(i)** Brutal or inhumane treatment of human subjects is never morally justified. **(ii)** Risks should be reduced to those necessary to achieve the research objective. It should be determined whether it is in fact necessary to use human subjects at all. Risk can perhaps never be entirely eliminated, but it can often be reduced by careful attention to alternative procedures. **(iii)** When research involves significant risk of serious impairment, review committees should be extraordinarily insistent on the justification of the risk (looking usually to the likelihood of benefit to the subject -- or, in some rare cases, to the manifest voluntariness of the participation). **(iv)** When vulnerable populations are involved in research, the appropriateness of involving them should itself be demonstrated. A number of variables go into such judgments, including the nature and degree of risk, the condition of the particular population involved, and the nature and level of the anticipated benefits. **(v)** Relevant risks and benefits must be thoroughly arrayed in documents and procedures used in the informed consent process.

3. Selection of Subjects. -- Just as the principle of respect for persons finds expression in the requirements for consent, and the principle of beneficence in risk/benefit assessment, the principle of justice gives rise to moral requirements that there be fair procedures and outcomes in the selection of research subjects.

Justice is relevant to the selection of subjects of research at two levels: the social and the individual. Individual justice in the selection of subjects would require that researchers exhibit fairness: thus, they should not offer potentially beneficial research only to some patients who are in their favor or select only "undesirable" persons for risky research. Social justice requires that distinction be drawn between classes of subjects that ought, and ought not, to participate in any particular kind of research, based on the ability of members of that class to bear burdens and on the appropriateness of placing further burdens on already burdened persons. Thus, it can be considered a matter of social justice that there is an order of preference in the selection of classes of subjects (e.g., adults before children) and that some classes of potential subjects (e.g., the institutionalized mentally infirm or prisoners) may be involved as research subjects, if at all, only on certain conditions.

Injustice may appear in the selection of subjects, even if individual subjects are selected fairly by investigators and treated fairly in the course of research. Thus injustice arises from social, racial, sexual and cultural biases institutionalized in society. Thus, even if individual researchers are treating their research subjects fairly, and even if IRBs are taking care to assure that subjects are selected fairly within a particular institution, unjust social patterns may nevertheless appear in the overall distribution of the burdens and benefits of research. Although individual institutions or investigators may not be able to resolve a problem that is pervasive in their social setting, they can consider distributive justice in selecting research subjects.

Some populations, especially institutionalized ones, are already burdened in many ways by their infirmities and environments. When research is proposed that involves risks and does not include a therapeutic component, other less burdened classes of persons should be called upon first to accept these risks of research, except where the research is directly related to the specific conditions of the class involved. Also, even though public funds for research may often flow in the same directions as public funds for health care, it seems unfair that populations dependent on public health care constitute a pool of preferred research subjects if more advantaged populations are likely to be the recipients of the benefits.

One special instance of injustice results from the involvement of vulnerable subjects. Certain groups, such as racial minorities, the economically disadvantaged, the very sick, and the institutionalized may continually be sought as research subjects, owing to their ready availability in settings where research is conducted. Given their dependent status and their frequently compromised capacity for free consent, they should be protected against the danger of being involved in research solely for administrative convenience, or because they are easy to manipulate as a result of their illness or socioeconomic condition.

(1) Since 1945, various codes for the proper and responsible conduct of human experimentation in medical research have been adopted by different organizations. The best known of these codes are the Nuremberg Code of 1947, the Helsinki Declaration of 1964 (revised in 1975), and the 1971 Guidelines (codified into Federal Regulations in 1974) issued by the U.S. Department of Health, Education, and Welfare. Codes for the conduct of social and behavioral research have also been adopted, the best known being that of the American Psychological Association, published in 1973.

(2) Although practice usually involves interventions designed solely to enhance the well-being of a particular individual, interventions are sometimes applied to one individual for the enhancement of the well-being of another (e.g., blood donation, skin grafts, organ transplants) or an intervention may have the dual purpose of enhancing the well-being of a particular individual, and, at the same time, providing some benefit to others (e.g., vaccination, which protects both the person who is vaccinated and society generally). The fact that some forms of practice have elements other than immediate benefit to the individual receiving an intervention, however, should not confuse the general distinction between research and practice. Even when a procedure applied in practice may benefit some other person, it remains an intervention designed to enhance the well-being of a particular individual or groups of individuals; thus, it is practice and need not be reviewed as research.

(3) Because the problems related to social experimentation may differ substantially from those of biomedical and behavioral research, the Commission specifically declines to make any policy determination regarding such research at this time. Rather, the Commission believes that the problem ought to be addressed by one of its successor bodies.

D. Links to Applicable Laws:

16. *Code of Federal Regulations Title 45 Public Welfare, Department of Human Services, Part 46 Protection of Human Subjects:* <http://www.hhs.gov/ohrp/policy/ohrpreulations.pdf>

2. Common Rule: <http://www.hhs.gov/ohrp/humansubjects/commonrule/index.html>

3. FDA: <http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm>

4. Policy Guide and Index: <http://www.hhs.gov/ohrp/policy/index/index.html>

E. Federal Wide Assurance (FWA):

FWA #: FWA00022305
Institution: Carrick Institute for Graduate Studies
Expires: 07/16/2020

OMB No. 0990-0278
Approved for use through August 31, 2017

Federalwide Assurance (FWA) for the Protection of Human Subjects

1. Institution Filing Assurance

Legal Name: Carrick Institute for Graduate Studies
City: Cape Canaveral State/Province: FL Country: USA

2. Institutional Components

List below all components over which the Institution has legal authority that operate under a different name. Also list with an asterisk (*) any alternate names under which the Institution operates.

NOTE: The Signatory Official signing this Assurance must be legally authorized to represent the Institution providing this Assurance and all components listed below.

Name of Component or Alternate Names Used	City	State (or Country if Outside U.S.)
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3. Statement of Principles

This Institution assures that all of its activities related to human subjects research, regardless of the source of support, will be guided by the following statement of principles governing the institution in the discharge of its responsibilities for protecting the rights and welfare of human subjects of research conducted at or sponsored by the institution. (indicate below)

The Belmont Report

4. Applicability

(a) This Assurance applies whenever this Institution becomes engaged in human subjects research conducted or supported by any U.S. federal department or agency that has adopted the U.S. Federal Policy for the Protection of Human Subjects (also known as the Common Rule), unless the research is otherwise exempt from the requirements of the Common Rule or the department or agency conducting or supporting the research determines that the research shall be conducted under a separate assurance.

(b) Optional: This Institution elects to apply the following to all of its human subjects research regardless of the source of support, except for research that is covered by a separate assurance:

The Common Rule (see section 3 of the Terms of the FWA for a list of U.S. federal departments and agencies that have adopted the Common Rule and the applicable citations to the Code of Federal Regulations)

5. Assurance of Compliance with the Terms of the Federalwide Assurance

(a) This Institution assures that whenever it engages in research to which this Assurance applies, it will comply with the Terms of the Federalwide Assurance (contained in a separate document on the Office for Human Research Protections (OHRP) website).

6. Designation of Institutional Review Boards (IRBs)

This Institution assures that it will rely upon only IRBs registered with OHRP for review of research to which this FWA applies. This institution (a) designates the following internal IRB(s) for review of research under this Assurance; or (b) does not have an internal IRB and designates the following external IRB for review of all research to which this FWA applies or, if multiple external IRBs are relied upon, the following external IRB that reviews the largest percentage of research to which this FWA applies.

NOTE: Institutions designating internal IRBs do not need to designate any of the external IRBs upon which it relies.

HHS IRB Registration Number	Name of IRB as Registered with HHS	Is the IRB Internal or External to the Institution?
IRB00006615	Carrick Inst for Graduate Studies IRB #1 - Neurology	I

7. Human Protections Administrator (e.g., Human Subjects Administrator or Human Subjects Contact Person)

First Name: Frederick Middle Initial: R Last Name: Carrick
Degrees or Suffix: D.C., Ph.D. Institutional Title: Professor of Clinical Neurology
Institution: Carrick Institute for Graduate Studies
Telephone: 321 868-6464 FAX: 321 868-6468 E-Mail: drfcarrick@gmail.com
Address: 203-894 Lake Drive
City: Cape Canaveral State/Province: FL Country: USA

8. Signatory Official (i.e., Official Legally Authorized to Represent the Institution)

I have read and agree to the Terms of the Federalwide Assurance.

I recognize that providing research investigators, IRB members and staff, and other relevant personnel with appropriate initial and continuing education and training about human subject protections will help ensure that the requirements of this Assurance are satisfied.

Acting officially in an authorized capacity on behalf of this Institution and with an understanding of the Institution's responsibilities under this Assurance, I assure protections for human subjects as specified above. The IRB(s) that this institution relies upon will comply with the Terms of the Federalwide Assurance when reviewing research covered by this Assurance and possess appropriate knowledge of the local context in which this Institution's research will be conducted.

All information provided with this Assurance is up-to-date and accurate. I am aware that false statements could be cause for invalidating this Assurance and may lead to other administrative or legal action.

Signature: Frederick R Carrick D.C., Ph.D.

Date: 07/16/2015

First Name: Frederick Middle Initial: R Last Name: Carrick

Degrees or Suffix: D.C., Ph.D. Institutional Title: Professor of Clinical Neurology

Institution: Carrick Institute for Graduate Studies

Telephone: 321 868-6464 FAX: 321 868-6468 E-Mail: drfrcarrick@gmail.com

Address: 203-894 Lake Drive

City: Cape Canaveral State/Province: FL Country: USA

9. FWA Approval

The Federalwide Assurance for the Protection of Human Subjects for Institutions Within the United States submitted to HHS by the above Institution is hereby approved.

Assurance Number: FWA00022305

Expiration Date: 07/16/2020

Signature of HHS Approving Official: Hal Blatt

Date: 07/16/2015

According to the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number. The valid OMB control number for this information collection is 0990-0278 . The time required to complete this information collection is estimated to average 30 minutes per response, including the time to review instructions, gather the data needed, and complete and review the information collection. If you have comments concerning the accuracy of the time estimate(s) or suggestions for improving this form, please write to: U.S. Department of Health & Human Services, OS/OCIO/PRA, 200 Independence Ave., S.W., Suite 336-E, Washington D.C. 20201, Attention: PRA Reports Clearance

F. List of IRB Members, their Abbreviated CV's and NIH PHRP Certificates

FR Carrick, Administrator

Kurt Kuhn, Chair

Linda Mullin, Vice Chair

Susan Esposito, Non-affiliated member

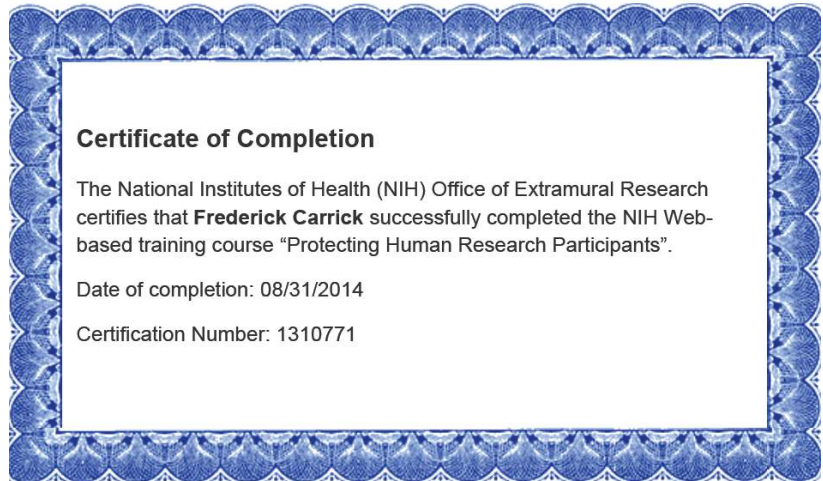
Rebecca Robillard, Non-scientific member

Sergio Azzolino, Member

Derek Barton, Member

Glen Zielinski, Member

Matt Anonucci, Member



I. FR Carrick, Administrator

Education:

- DC Chiropractic, Canadian Memorial Chiropractic College
- PhD Education, Walden University
- BS University of Manitoba

Certifications, Board Certifications & Fellowships:

- Board Certified Chiropractic Neurologist, (DACAN, DABCN, DACNB)
- Diplomate of the American Academy of Pain Management (DAAPM)
- Fellow of the Royal College of Physicians Functional (FRCPN)
- Fellow of the American College of Clinical Neurology (FACCN)
- Fellow Australoasian Academy of Functional Neurology (FAAFN)
- Fellow of the European Chiropractic Academy of Chiropractic (FEAC) (Neurology)
- Fellow of the American College of Functional Neurology (FACFN)
- Fellow of the American College of Clinical Neurology (FABVR)
- Fellow of the American Board of Electrodiagnostic Specialties (FABES)
- Fellow of the American Board of Childhood Developmental Disorders (FABCDD)
- Fellow of the International College of Chiropractors (FICC)

Additional Professional Experience:

- Dean of Education for Carrick Institute of Graduate Studies
- Professor of Neurology, Carrick Institute for Graduate Studies
- Professor Emeritus of Neurology, Parker College
- Distinguished Post Graduate Professor of Clinical Neurology, Logan College
- Professor of Clinical Neurology, Carrick Institute



II. Kurt Kuhn, Chair

Education:

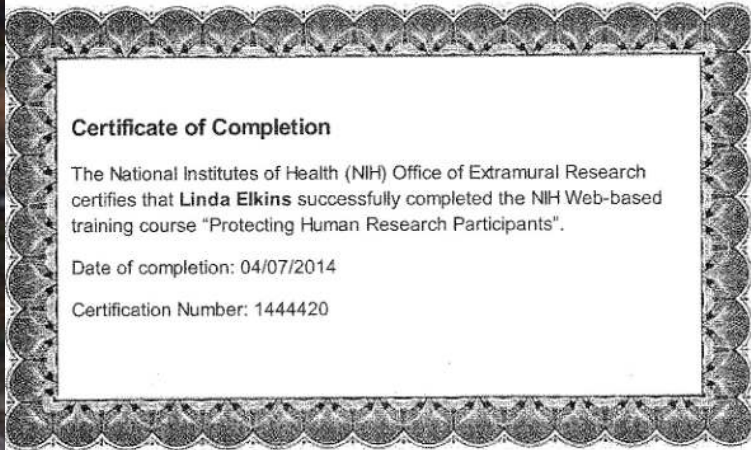
- DC Chiropractic, Palmer College of Chiropractic
- PhD Education, Capella University
- MS Advanced Clinical Practice, National University of Health Science
- MS Management, Purdue University
- BS University of the State of New York

Certifications, Board Certifications & Fellowships:

- Board Certified Chiropractic Neurologist (ACNB)
- Board Certified Neurofeedback (BCIA)
- Certified Electrodiagnostics (ACNB)
- Certified Chiropractic Spinal Trauma (ICA)
- Fellow, American College of Functional Neurology
- Fellow, American College of Electrodiagnostic Specialties
- Virtual Fellowship EEG, FSU
- IRB Chair & Human Research Curriculum (23 Modules), CITI

Additional Professional Experience:

- Reviewer, Journal of Chiropractic Medicine
- Delphi Panel Member for Chronic Pain, CCGPP
- Mentor, BCIA-EEG
- Preceptor, Palmer College of Chiropractic
- Post Graduate Education Instructor, Palmer College of Chiropractic
- Biology, Nutrition & Economics Instructor at Qwest, AIC, Hamilton Colleges and UIU
- 32 years clinical practice



III. Linda Mullin, Vice Chair

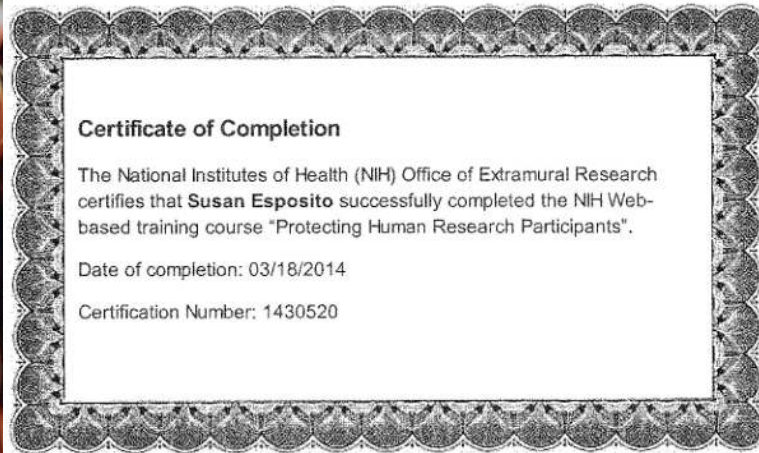
- DC Chiropractic, Life Chiropractic College
- BA Psychology, Eastern CT University

Certifications, Board Certifications & Fellowships:

- Diplomate Gonstead Studies Society
- Fellow Gonstead Clinical Studies Society
- Diplomate Academy of Chiropractic Family Practice
- Fellow International Chiropractic Pediatric Association
- Certificate Academy of Chiropractic Family Practice

Additional Professional Experience:

- Professor Life Chiropractic College
- Past Chair and current IRB member for Life Chiropractic College
- Editorial Board Member of Journal of Pediatric, Maternal & Family Health, Frontiers Journal, International Journal of Chiropractic
- 22 years clinical practice



IV. Susan Esposito, Non-Affiliated Member

Education:

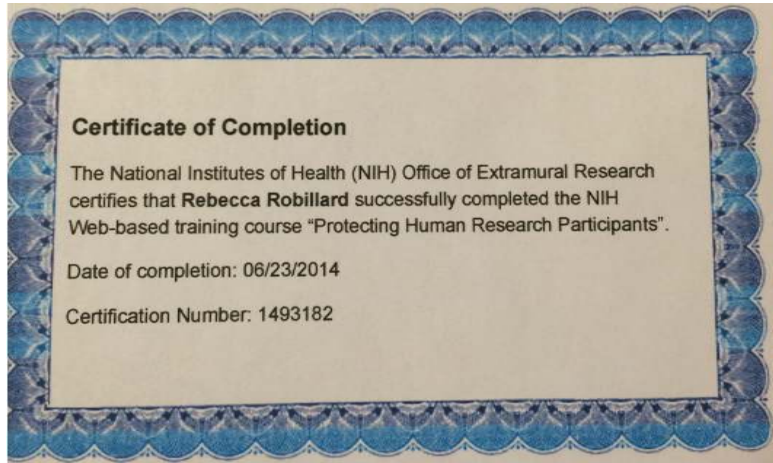
- DC Chiropractic, Life Chiropractic University
- BS Business Management, LaSalle University

Certifications, Board Certifications & Fellowships:

- Board Certified Chiropractic Neurologist (ACNB)
- Fellow, American College of Functional Neurology
- Fellow, America College of Electrodiagnostic Specialities

Additional Professional Experience:

- Staff Chiropractic Functional Neurologist at Life Functional Neurology
- Life University Associate Professor for Chiropractic Sciences
- Chair, ACA's Council on Electrodiagnostics
- Electrodiagnostic Technologist
- Educational Coordinator, Gary Null Health Group
- 10 years clinical practice



V. Rebecca Robillard, Non-scientific Member

Education:

- Student Biomedical Research and Lab, Eastern Florida State College
- AA Mathematics, Brevard Community College
- Rockledge High School

Additional Experience:

- Assistant Carrick Institute
- Building Bodies Fitness Center
- Volleyball Captain for Junior/Senior High school with Leadership Award
- Volunteer for Cancer, heart and diabetes awareness
- Skin cancer survivor



VI. Sergio Azzolino

Education:

- DC Chiropractic, Life-West Chiropractic College
- BS San Francisco State University

Certifications, Board Certifications, & Fellowships:

- Board Certified Chiropractic Neurologist (ACNB)
- Fellow American College of Functional Neurology
- Diplomate American Academy of Pain Management
- Fellow American Board of Childhood Developmental Disorders

Additional Professional Experience:

- Vice President, American Chiropractic Neurology Board
- Vice Chair - California Board of Chiropractic Examiners
- Assistant Professor of Clinical Neurology, Carrick Institute
- 19 Years clinical practice



VII. Derek Barton

Education:

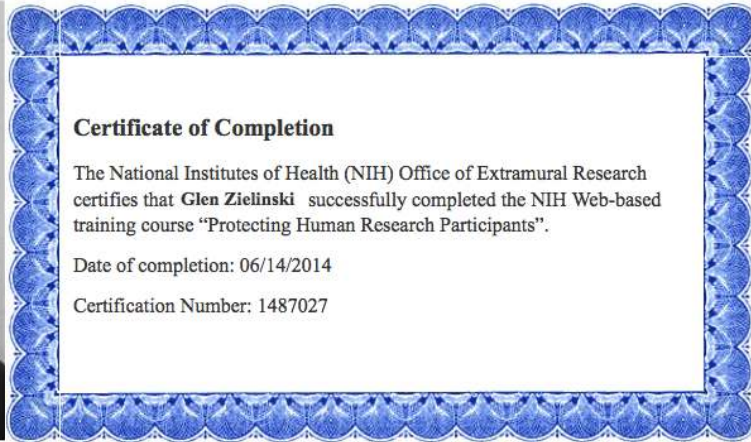
- Doctorate of Chiropractic, Life Chiropractic University
- BS, Mechanical Engineering, University of Wisconsin, Platteville

Certifications, Board Certifications & Fellowships:

- Board Certified Chiropractic Neurologist (ACNB)

Additional Professional Experience:

- Clinical Assistant Professor of Neurology, Carrick Institute of Graduate Studies
- Clinician, Provider Relations Liaison, Life Functional Neurology Center
- Researcher Associate, Life University
- Adjunct Faculty, Life University
- 4 years clinical experience



VIII. Glen Zielinski

Education:

- DC Chiropractic, Parker College of Chiropractic
- BS Anatomy, Parker College of Chiropractic
- BA Communications, Simon Fraser University

Certifications, Board Certifications & Fellowship:

- Board Certified Chiropractic Neurologist (ACNB)
- Fellow American College of Functional Neurology

Additional Professional Experience:

- Assistant professor of clinical neurology with the Carrick Institute
- Instructor Brain Chemistry, Apex Energetics
- Adjunct Clinical Faculty, Northwestern Health Sciences University
- Adjunct Clinical Faculty, National College of Naturopathic Medicine
- Received numerous awards, including the Parker College Board of Trustees Award for Excellence in Diagnosis
- 14 years of clinical experience



IX. Matt Antonucci

Education:

- DC Life University College of Chiropractic
- Central Connecticut State University

Certifications, Board Certifications & Fellowships:

- Master's of Neuroscience
- Fellow, American Board of Neurochemistry and Nutrition
- Fellow, American Board of Childhood Developmental Disorders
- Fellow, American Board of Vestibular Rehabilitation
- Fellow American Board of Functional Neurology
- Diplomate, American Chiropractic Neurology Board

- **Additional Professional Experience:**
 - Frontiers in Public Health, Review Editor
 - NueroLogic Enterprise, LLC, Consultant and contracted locum neurologist
 - Life Functional Neurology Center
 - International Association of Functional Neurology and Rehab, Planning Committee member

G. Standard Forms:

- 1.Application for exemption from IRB
- 2.Application for expedited approval
- 3.Application for case study
- 4.Standard application for approval of human research project
- 5.Research amendment form
- 6.Protocol renewal form
- 7.Adverse events form
- 8.Sample consent form
- 9.Sample assent form

H. Bibliography used in the creation of this document:

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Additional SOP's Reviewed from:

Yale University: <http://www.yale.edu/hrpp/policies/index.html>