ASPIRUS WAUSAU HOSPITAL
Institutional Review Board
Human Research Protection Program
(IRB – HRPP)

Investigator Manual

for

Human Subject Research

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Investigator Manual

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Investigator's Manual
For Research Involving Human Subjects

Note: Please read this manual carefully. It contains important information that will help you in conducting research involving human subjects.

PREPARING FOR IRB SUBMISSION

Purpose of this Manual

This manual is intended as a guide for all who plan to carry out research, whether funded or not funded, involving the participation of human subjects. It provides basic information about what materials are needed to apply for human subjects approval and how to do it.

All research that is conducted by an individual in connection with his or her institutional responsibilities and/or which involves the use of any of Aspirus' property or facilities must conform to a standard of ethics reflected in specific regulations of the United States Department of Health and Human Services (DHHS) in order to assure that the rights and welfare of human subjects are protected. Aspirus Wausau Hospital has a Federal Wide Assurance (FWA) with DHHS, which describes Aspirus policies and procedures for the protection of human subjects in all research that involves them. Copies of the Federal Wide Assurance and of the Federal Regulations governing research involving human subjects may be obtained from the Aspirus Wausau Hospital's Institutional Review Board (AWH IRB) Office or at the Aspirus Wausau Hospital IRB website http://www.aspirus.org/hospitalsClinics/index.cfm?catID=2&subCatID=17&pageID=203

Introduction

Any member of the Aspirus community, anyone using Aspirus, Inc. facilities or any institution that has designated AWH IRB as their IRB of record, must have their research with human subjects, reviewed and approved by the Aspirus Wausau Hospital's Institutional Review Board (referred to hereafter as the IRB). The purpose of this review is to allow the IRB to evaluate the "risk to benefit ratio" of the research. The IRB's **only** interest is in protecting the safety, welfare, privacy, rights of human research subjects and maintaining compliance with federal research regulations. It is not the IRB's objective to pass judgment on other aspects of the research except as it relates to this ratio. However, it is within the IRB's purview if it determines the need to appraise research methodology as it relates to human subjects protection. To this end, principal investigators shall prepare protocols giving complete descriptions of the proposed research.

The most important concerns of the IRB are to assure subjects' safety, preserve subjects' anonymity and confidentiality, and assure that participation is voluntary. Another concern is the desire for subjects to be fully informed of the procedures to be employed in the study and of possible adverse effects.

What Is Human Research?

Human Research is defined by the Department of Health & Human Services (DHHS) regulations 45 CFR 46.102(d), 45 CFR 46.102 (f) and defined in Food and Drug Administration (FDA) regulations at 21 CFR 46.102 (c), 21 CFR 56.102 (e) and 21 CFR 812.3 (p). Please review Human Research Checklist on AWH IRB website or Appendix A in this document to assist you with determination as to if your project is human research.

Activities Requiring IRB Review

There is sometimes a question of whether a planned activity is "**research**" and, therefore, requires IRB review and approval. The DHHS Federal policy defines research as "a systematic investigation, including research development, testing and evaluation, designed to develop or to contribute to generalizable knowledge." All research activities involving human subjects must be approved by an IRB **prior to initiation** of the study. A **human subject** is defined as a living individual about whom an investigator obtains data through intervention or interaction with the individual, or identifiable private information.

Specific criteria that can be used to determine whether a planned activity is research include:

1) The testing of a hypothesis or question for which an answer requires more information. **Example:** a survey of nursing students' job expectations to be compiled with data from several institutions with the intent to publish the results.

2) The prospective or retrospective collection of data from human subjects/patients with the prior intent to publish such results. **Example**: review of medical records and collection of data to determine specific patient outcomes for publication in a scientific journal.
3) The use of a standard procedure or an approved drug if its use is influenced by any consideration other than the direct welfare of the individual. For example:
    1. a selection between different, although widely-accepted, procedures or therapies according to a predetermined plan such as randomization; or
    2. the administration of a standard procedure of an approved drug to a healthy "control" subject.

    Example: assigning 20 patients randomly to receive one of two drugs and comparing outcomes.
4) the use of an experimental (investigational) drug, biologic, or device (e.g., a drug that is the subject of a FDA-approved investigational new drug (IND) exemption or a device that is not FDA approved). **Example**: a clinical trial comparing an investigational drug to a standard treatment.

Subject recruitment strategies and materials also require IRB approval prior to distribution, publication, or promotion. In addition, the IRB provides continual review of research studies through an annual review process and the review of serious adverse events.

Emergency use of an investigational drug or device must be reported to the IRB within 5 working days. However, before the emergency use of a test article without prior approval is allowed, FDA regulations (21 CFR 50.23) require that specific conditions exist (see IRB Emergency Use Policy or federal regulation) and are documented in writing. Continued use of such a product requires submission for full review by the IRB.

Activities That May Require IRB Review

Innovative Practice vs. Research

Innovative or newly-introduced clinical procedures or therapies do not require IRB review and approval except when they involve "research" as defined by the above criteria. An innovative clinical practice is an intervention designed solely to enhance the well-being of an individual patient or client. The purpose of an innovative clinical practice is to provide diagnosis, preventative treatment, or therapy to particular individuals. The introduction of innovative procedures or therapies into clinical practice (i.e., independent of a research activity approved by the IRB) should be reviewed with the applicable institutional personnel (i.e., department chair, etc.).

Quality Improvement Projects vs. Research

Quality assurance and/or improvement projects do not require IRB review and approval except when they involve "research" as defined by the above criteria. Precise definitions to permit the distinction between research studies and quality projects are difficult and have not been established. In general, a quality assurance project is a project that is focused primarily on improving patient care within a given patient care environment [e.g., hospital or health care organization] and, as such, the outcome of the project may not be generalizable to other patient care environments. Publication of a quality assurance project does not, per se, render that project "research"; however, if the outcome of a quality assurance project is published, attention should be given to avoiding the terminology "research" in the publication. Listed below are questions directed at providing guidance in distinguishing quality assurance projects from research:

- If you were told, in advance, that you couldn't publish the results of the proposed study, would you conduct the study anyway? Yes or No – if no, the study requires prior review and approval by the IRB.
- Is there a commitment, in advance of data collection, to a corrective plan given any one of a number of study outcomes? Does the principal investigator of the study have both clinical supervisory responsibility and the authority to impose change? Yes or No – if no to either question, the study requires prior review and approval by the IRB.
- Is the research being sponsored/funded by an external agency? Yes or No – if yes, the study MAY require prior review and approval by the IRB
- Does the proposed project involve the prospective assignment of patients to different procedures or therapies based on a predetermined plan such as randomization? Yes or No – if yes, the project requires IRB review and approval.
- Does the proposed project involve a "control group" in whom the therapeutic or study intervention is intentionally withheld to allow an assessment of its efficacy? Yes or No – if yes, the project requires IRB review and approval.
- Will the study intervention be delivered in a blinded fashion wherein neither the physician nor the patient knows to whom the study intervention or comparative intervention (e.g., placebo, standard care) was given? Yes or No – if yes, the project requires IRB review and approval.

- Is the assessment of outcome blinded to the study intervention for the purpose of establishing the efficacy of the intervention? Yes or No – if yes, IRB review and approval is required.
- Does the proposed project involve the prospective evaluation of a drug, biologic, or device that is not currently approved for general use by the FDA (i.e., to include off-label indications)? Yes or No – If yes, IRB review and approval is required
- Will patients involved in the proposed project be exposed to additional risks or burdens (other than the completion of a patient satisfaction surveys) beyond standard clinical practice in order to make the results of the study generalizable? Yes or No – if yes, IRB review and approval is required.

Obligations As An Investigator Prior To Review

If you plan to engage in research involving human subjects (as defined in the Federal Policy for the Protection of Human Subjects, 45 CFR Part 46), you are required to:

- Complete appropriate education and training in the protection of human research subject, initially and annually.
- Review Aspirus Wausau Hospital IRB SOP – "Investigator(s) & Research Staff Responsibilities"
- Complete the "Investigator Agreement" form
- Complete the "Affirmation of Integrity" form
- Complete a "Financial Conflict of Interest" form
- Submit a resume or Curriculum Vitae (CV)
- Prepare and Submit a IRB application along with the Protocol for review prior to starting the project

Writing An Investigator Protocol

Typically, the sponsor of the Human Research will provide a protocol, which is a detailed plan of why the research is being done and how it will be conducted. If you are an investigator sponsoring or leading your own Human Research you will be expected to create and submit a protocol for the IRB to review. You may use the "protocol template" to assist you in protocol development and writing. This template includes the sections at a minimum the IRB expects to see included. Here are some key points to remember when developing a protocol:

- The "Template" serves only as guidance to investigators when developing a Human Research Protocols for submission to the IRB. Remove the instructions on what to include in italics (e.g. Describe the purpose, specific) from your final protocol. If you are a new investigator, it is recommended that you work with a faculty advisor or mentor in developing your protocol.
- When writing a protocol, always keep an electronic copy of the final IRB approved protocol. You may need to modify this copy and submit it to the IRB with tracked changes, if future amendments/changes need to be made to the protocol. Modify the version date with each modification to the protocol.
- If you believe your activity may not be Human Research, contact the IRB office prior to developing your protocol for guidance on what to include.
- Note, that depending on the nature of your research (e.g. retrospective chart review), certain sections of the protocol template (e.g. data safety monitoring) may not be applicable. Remove sections that are not applicable to your type of Human Research.

Create Consent Document

Typically, the sponsor of Human Research will provide a sample informed consent document which provides the potential subject important information to consider before deciding whether or not to participate in the Human Research. You are expected to ensure the sponsor-provided informed consent document has the required elements per regulations, has local contact information, and include IRB suggested language and, for clinical trials, include Good Clinical Practice required items. If you are not working with a sponsor or a sample informed consent document is not provided, you will need to create an informed consent document. You may use the TEMPLATE" located on the IRB website to assist you in development and writing.

You must date your informed consent to ensure that you use the most recent version approved by the IRB when consenting subjects. Always keep an electronic copy of the final IRB approved consent document. You may need to modify this copy and submit it to the IRB with tracked changes, if future amendments/changes need to be made to the informed consent document. Modify the version date with each modification to the consent.

If you have questions on creating your informed consent document or other related consent documents such as assent documents, short forms, information sheets, or telephone scripts, please consent the IRB Office for assistance at lorisc@aspirus.org or at 715-897-1516.

HIPAA

The federal law called the Privacy Rule of the Health Insurance Portability & Accountability Act (HIPAA) requires authorization (permission) to be obtained to use or share identifiable health information for research purposes from the subject or a waiver from this requirement is granted for the Human Research by institution's Privacy Board. The Aspirus Wausau Hospital IRB has a dual role and also serves as the Privacy Board.

The DHHS Office for Civil Rights defines when the health information is considered identifiable under regulation 45 CFR 164.514 (b) and criteria that must be met to permit a waiver of authorization 45 CFR 164.512. If your Human Research will collect and/or share any of the listed identifiable items with the subject's health information and you do not meet the criteria for a waiver of authorization, you will be expected to include a HIPAA authorization to participate in the Human Research. To request a waiver of HIPAA authorization you will need to complete the applicable forms which can be found on the AWH IRB website.

If you need to create a HIPAA authorization document, start with the TEMPLATE CONSENT which contains the HIPAA Authorization towards the end of the document located under the IRB forms section of the IRB website.

IRB SUBMISSION and REVIEW

Submissions

New Investigator's please contact the AWH IRB Office at (715) 847-2569 to acquire access to the IRB's electronic submission program CYBERIRB. The IRB will provide you with instructions for the program, a username and password. Within CYBERIRB you will then complete the applicable IRB application form, attaching all requested supplemental and supporting documents.

Investigators whom have previously submitted human research for review in hard paper copies if you don't already have access to CYBERIRB you will also need to contact the IRB Office to acquire access and instructions.

All Investigators & Research staff should review AWH IRB policies/procedures for Initial, Modification, Continuing Review, Adverse events/unanticipated problems, Close of study procedures within AWH Onbase or you may request a CD from the IRB.

An IRB Meeting Agenda Timeline is provided on the IRB website at http://www.aspirus.org/irb/index.cfm?catID=11&subCatID=62&pageID=528&pageTitle=Investigators,-Research-Staff,-&-IRB-Members

New studies and renewals are due 4 weeks prior to the scheduled meeting date. All other study requests are due 2 weeks prior to the scheduled meeting date.

Should there be any questions relative to completing the applicable IRB submission form you may review the IRB newsletter, which can be found in the IRB website or you may call the IRB Office at 715-847-2569.

Application Fee For Submission

The IRB Office will invoice a fee for all industry sponsored (research sponsored by for-profit-organizations) study submissions, and continuing reviews. The initial submission fee a new study submission for convened or expedited review is $ 2,000 and $1,000 for continuing review.

Invoices are sent regardless of IRB determination and payment is due 30 days from receipt. As an investigator, you are responsible for ensuring these fees are covered in your Clinical Trial Agreement with the sponsor.

Types of IRB Review

Submitted activities may fall under one of the following types of IRB review:

- **Not "Engaged":** DHHS Office of Human Research Protections (OHRP) defines an institution as engaged in human research when its employees or agents for the purposes of the research obtain: (1) data about the subjects of the research through intervention or interaction with them (2) identifiable private information about the subjects of the research; or (3) the informed consent of human subjects for the research. For example, if an Aspirus physician collects a blood sample for genetic research study being conducted at another institution and has the

informed consent obtained by the other institution and does not collect data about the subject for the research then Aspirus would not be engaged in the Human Research. Contact the IRB Office in cases where it's unclear whether or not you are engaged in Human Research.

- **Not "Human Research":** Activities must meet the DHHS or FDA definition of "research" involving "human subjects" for the activity to fall under IRB oversight. Activities that meet neither definition of Human Subject Research are not subject to IRB oversight or review.
- **Exempt:** Certain categories of Human Research may be exempt from regulation but require IRB review. It is the responsibility of the IRB, not the investigator, to determine whether Human Research is exempt from IRB review. The IRB Exempt form lists the categories of research that may be exempt. This form should be filled out and submitted to the IRB Office for determination.
- **Expedited:** Certain categories of non-exempt Human Research may qualify for review using the expedited procedure. Review the IRB's Initial Application form for the categories of research that may be reviewed through the expedited process. The research must meet at least one or more of the categories and be considered "minimal risk" as defined within that form.
- **Convened/Full Board IRB:** Research that does not qualify for exempt or expedited review must be reviewed by the convened IRB.

Review Process

Exempt: Is determined upon receipt of the IRB exempt request form, protocol & any other related materials to the IRB office. The IRB Coordinator will review the submission materials to determine if the project fulfills one or more of the exempt status criteria. If one or more are applicable then it will be forwarded to the IRB Chair or authorized designee for the final determination of exempt status. Upon determination a written notification will be sent to the Investigator. No further review would then be required, unless there was a change to the project.

Expedited: Review is conducted upon receipt of the applicable IRB request form, protocol, informed consent & any other related materials to the IRB Office with a determination being made in a timely manner. The process involves the IRB Coordinator screening for completeness, accuracy, and then making the initial determination if expedited review is applicable. After that it is forwarded to an Expedited reviewer (IRB member) for review and final determination to approve, request modifications to secure approval, or defer for full board review.

Convened/Full Board – New Study: Submission is requested 4 weeks prior to the monthly scheduled IRB meeting date that the investigator wishes to have the project reviewed. Upon receipt of the applicable IRB request form, protocol, informed consent, & any other related materials submitted, the IRB Coordinator will screen for completeness and accuracy. It will then be placed on the appropriate IRB meeting agenda in accordance with the IRB submission timeline located on the AWH IRB website.

Prior to the meeting date the new study requiring a convened/full board IRB review is assigned two primary reviewers with at least one of them being a physician. Although the full IRB is involved in review of the research, the primary reviewers perform a more thorough review of all research materials. The study is presented at an IRB meeting by the principal investigator. Following discussion of the research, the convened IRB members will make a determination to approve, request modifications to secure approval, table research, defer or disapprove.

Convened/Full Board – continuing review: Submission is requested 4 weeks prior to monthly IRB meeting date of review for Renewals of protocol and 2 weeks prior for amendments, closures, adverse events, etc. Upon receipt of the applicable IRB request form and related study materials to the IRB Office the IRB Coordinator will screen for completeness and accuracy. It will then be placed on the appropriate IRB meeting agenda for review. The convened IRB members will review, discuss and make a determination to approve, request modifications to secure approval, table research, defer or disapprove

Exempt, Expedited or Convened IRB determinations will be provided in writing to the Investigator within a timely manner (generally within one week). If you have not received correspondence from the IRB Office, please feel free to contact the IRB Office for a status update at (715) 847-2569. Investigator's then have an opportunity to resubmit or respond to a disapproval of a study (if applicable).

IRB MEETINGS

The Aspirus Wausau Hospital Institutional Review Board (AWH-IRB) meetings are held the 3rd Tuesday of every month from 7:30am until 9 am in the AWH Medallion Room or as determined by the Chairperson and members are unless otherwise notified.

The IRB Chair or Vice Chair in his/her absence will conduct the meeting. The IRB Recording Secretary or IRB staff will record minutes of the meeting. All IRB members are expected to have reviewed all research study materials submitted prior to the meeting, which they will have been provided at a minimum of 1 week prior to the meeting date. For new study submissions, the PI will present their project that was submitted and address any questions the IRB members may have. The designated Research Coordinator will present all other study submissions and address any questions from IRB members. The Full board then discusses the study and issues raised by the study during the meeting. Once all questions are addressed the full board then votes. Studies may be approved, approved with modifications, or deferred. A quorum of 51% of the total IRB members, with at least one member whose primary focus is non-scientific, must be present for any business to be conducted. After all research submitted has been reviewed, discussed and voted upon the meeting will be adjourned with the PIs then being notified of the outcome from the meeting regarding their submissions.

Determinations

Approval: In accordance with the Code of Federal Regulations, the IRB will only approve research that meets the following criteria:

- All risks are reasonable in relation to anticipated benefits
- Risk to human research subjects is minimized and the benefit/risk ratio to maximized
- Selection of research subjects is equitable
- Human research subjects are adequately informed of the risks and benefits involved
- Informed consent is obtained in advance of research participation
- Research plan provides monitoring of data to ensure safety of human subjects

- Privacy of human research subjects is protected and the confidentiality of data is maintained
- Rights of human research subjects who may be vulnerable to coercion are protected.

Modifications Required to Secure Approval: Made when IRB members require specific modifications to a protocol before approval can be finalized.

Tabled: Made when the IRB cannot approve the research at a meeting for reasons unrelated to the protocol, such as loss of quorum, or PI not available to present new study submission. When taking this action, the IRB automatically schedules the protocol for the next meeting.

Deferred: Made when the IRB determines that the board is unable to approve a protocol and the IRB suggests modifications that might make the research approvable. When making this motion, the IRB describes its reasons for this decision, describes modifications that might make the research approvable, and gives the investigator an opportunity to respond to the IRB in person or in writing.

Disapproval: Made when the IRB determines that it is unable to approve a protocol and the IRB cannot describe modifications that might make the research approvable. When making this motion, the IRB describes its reasons and gives the investigator an opportunity to respond to the IRB in person or in writing. Disapproval of a study may not be overturned by any other person or committee.

POST IRB REVIEW and APPROVAL

After IRB Review

The IRB will provide you with a written decision indicating that the IRB has approved the Human Research, require modifications to secure approval, have deferred, or has disapproved the Human Research.

- If the IRB approved: Research may commence once the IRB letter of approval is received and all other organizational approvals have been met. IRB approval is good for a limited period of time, which is noted in the approval letter.
- If the IRB requires modifications to secure approval and you accept the modifications, then you make the requested modifications and submit them to the IRB Office. The IRB Will then issue the approval letter. If you don't respond to the IRB, the offer of approval will be withdrawn.
- If the IRB defers then the IRB will provide statement of reason for disapproval and give you an opportunity to responds in writing.
- If the IRB disapproves the IRB will provide a statement of the reasons for disapproval and give you an opportunity to respond in writing. If you do not respond within 30 days, the IRB will require a new protocol submission.

In all cases, you have the right to address your concerns (appeal) to the IRB directly at an IRB meeting.

Obligations of an Investigator After IRB Approval

- Do not start Human Research activities until you have the final IRB approval letter in your possession.
- Personally conduct or supervise the Human Research
    1) Conduct the research in accordance with the relevant current protocol as approved by the IRB, IRB policies, institutional policies and applicable federal, state, and local regulations regarding human subject protection
    2) For clinical trials, conduct the research in accordance with International Conference on Harmonisation (ICH) E6 Good Clinical Practice Consolidated Guidance.
    3) When required by the IRB, ensure that consent or permission is obtained in accordance with the relevant protocol, as approved by the IRB and documented (if required)
    4) Do not modify the research without prior IRB review and approval unless necessary to eliminate apparent immediate hazards to subjects
    5) Supervise all study support staff and ensure they are adequately trained for their roles and delegated responsibilities
    6) Protect the rights, safety, and welfare of subjects involved in research
- Submit to the IRB:
    1) Proposed modifications, adverse events, continuing reviews, deviations, etc using the appropriate IRB application form located within CYBERIRB or under forms on the IRB website.
    2) Contact the IRB Office at 715-847-2569 should you have any questions about these forms
- Do not accept or provide payments to professionals in exchange for referrals of potential subjects
- Maintain study documentation and signed and dated consent documents
- When subjects withdraw from FDA-regulated clinical trials follow FDA guidance on data retention http:www.fda.gov/downloads/regulatoryinformation/guidances/UCM126489.pdf
- For FDA-regulated research involving investigational drugs comply with the following FDA regulations: 21 CFR 312.7, 312.57, 312.59, 312.60, 312.61, 312.64, 312.66, 312.68, and 312.69
- For FDA-regulated research involving investigational devices comply with the following FDA regulations: 21 CFR 812.7, 812.100, 812.110, 812.145, and 812.150
- For research involving clinical trials, comply with the International Council on Harmonization-Good Clinical Practice Guidelines (E6) Section 4.

Informed Consent Process

The process of obtaining informed consent follows the basic ethical principle of the Belmont Report respect for persons and the Federal regulations. There are three main steps for obtaining informed consent: 1) providing information, 2) ensuring understanding and 3) obtaining voluntary agreement to participate.

Please review the AWH Informed Consent Policy and Procedure as well as the AWH Non-English Informed consent policy (included in this manual)

When obtaining informed consent the following documentation is required:

- The subject, legally authorized representative (in the case of adults with diminished decision making capacity), or parent/guardian in the case of minors, prints their name and signs and dates the consent document
- The individual obtaining consent signs and dates the consent document
- For a subject, legally authorized representative, or parent/guardian in the case of minors, whom are unable to read the consent due to visual impairments or illiteracy/limited English proficiency, and/or whenever required by the IRB or the sponsor, a witness must be present to the entire oral presentation and prints their name and signs and dates the consent document attesting to witnessing the entire consent process. The witness should be provided a copy of the informed consent document to follow along during the process to ensure what was verbally relayed is accurate.
- A copy of the signed and dated consent document is to be provided to the subject, legally authorized representative or parent/guardian in case in minors. A copy is also to be placed in the subject's medical record. The original signed and dated consent document is maintained with other study/regulatory documents.
- Please refer to the AWH Informed consent policy and procedure and the AWH Informed consent
- When subjects are approached for considering participation in a research study and the informed consent process is performed, an entry is required in the patient's medical record recording if the patient declined or consented. If the subject consented, provide a summary of the details surrounding the informed consent discussion in the patient's medical record.

OTHER INFORMATION

Emergency Use of an Investigational Drug, Biologic or Device

Refer to AWH policy/procedure for Emergency use of an unapproved drug or device in a life-threatening situation without prior IRB Review as referred to as research by the FDA.

Audits

AWH IRB conducts either for cause or routine audits of investigator consent documents, study conduct, and study documentation. If the IRB or IRB Chair has information (i.e. a subject complaint) that the study is potentially not being conducted in accordance with the IRB requirements for protecting research subjects, an inquiry or audit may take place to see if the allegations are founded.

Furthermore, as indicated in the federal regulations 45 CFR 46.109 (e) and 21 CFR 56.109 (f), the IRB has the authority to observe or have a third party observe the consent process and research.

ASSISTANCE PROVIDED BY IRB AND STAFF

The Committee and staff are available to:

- Discuss human subjects issues relevant to your research such as risks and benefits, informed consent, recruiting subjects, advertising, privacy and confidentiality

- Pre-review your research protocol and consent form to identify potential issues and suggest ways to address them prior to IRB review
- Provide educational information on the protection of human research subjects
- Provide guidelines and research protocol forms
- Prepare needed documents, i.e., Certification of Assurances
- Provide the forms and assistance to submit:
    - Changes to your research or consent form after research is approved
    - Progress reports for the IRB review to continue your research
    - Reports of unanticipated or adverse effects
    - The final report

IRB CONTACT

For more information about specific IRB requirements and to obtain IRB submission forms, contact Lori Scheller, Human Research Protections Coordinator at 847-2569 or lorisc@aspirus.org. In addition, the IRB policies and forms are available on the Aspirus Wausau Hospital IRB website.

APPENDICES

TAB 1: Investigator Forms to be completed

Investigator Agreement
Affirmation Of Integrity
Investigator's Financial Disclosure Form
Supplemental Research Activity Form
Human Subject Protection Education/Training

Aspirus Wausau Hospital, Inc.
Institutional Review Board

Investigator Agreement

Name of Investigator: _____

Name of Institution Providing IRB Oversight: **Aspirus Wausau Hospital**

OHRP Federal-Wide Assurance Number: **FWA00002047**

Research Covered Under This Agreement: **Research Activities Involving Human Subjects**

1. The above-named *Investigator* has reviewed *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*, the U.S. Department of Health and Human Services (DHHS) regulations for the protection of human subjects at 45 CFR 46, the Assurance referenced above, and the relevant institutional policies and procedures for the protection of human subjects.

2. The Investigator understands and hereby accepts the responsibility to comply with the standards and requirements stipulated in the above documents and to protect the rights and welfare of human subjects involved in research conducted under this Agreement.

3. The Investigator will comply with all other National, State or local laws or regulations that may provide additional protection for human subjects.

4. The Investigator will abide by all determinations of the IRB designated under the above Assurance and will accept the final authority and decisions of the IRB, including but not limited to directives to terminate participation in designated research activities.

5. The Investigator will complete any training required by the IRB prior to initiating research covered under this Agreement.

6. The Investigator will report promptly to the IRB proposed changes in the research conducted under this agreement. The investigator will not initiate changes in the research without prior IRB review and approval, except where necessary to eliminate apparent immediate hazards to subjects.

7. The Investigator will report immediately to the IRB any unanticipated problems in research covered under this Agreement that involve risks to subjects or others.

8. The Investigator will seek, document and maintain records of informed consent from each subject or the subject's legally authorized representative as required under HHS regulations (or other international or national equivalent) and stipulated by the IRB.

9. The Investigator acknowledges and agrees to cooperate in the IRB's responsibility for initial and continuing review, record keeping, reporting and certification. The Investigator will provide all information required by the IRB in a timely fashion.

10. In conducting research involving FDA-regulated products, the investigator will comply with all applicable FDA regulations and fulfill all investigator responsibilities (or investigator-sponsor responsibilities, where appropriate), including those described at 21 CFR 312 and 812.

11. The investigator will not enroll subjects in research under this Agreement prior to its review and approval by the IRB.

12. Emergency medical care may be delivered without IRC review and approval to the extent permitted under applicable Federal regulations and state law. However, such medical care may not be included as part of Federally-supported research.

13. This Agreement does not preclude the investigator from taking part in research not covered under the Agreement.

14. The investigator acknowledges that his/her primary responsibility is to safeguard the rights and welfare of each research subject, and that the subject's rights and welfare must take precedence over the goals and requirements of the research.

Signatures:

Investigator: _____ Date: _____

IRB Institutional Official: _____ Date: _____

ASPIRUS WAUSAU HOSPITAL
INSTITUTIONAL REVIEW BOARD

AFFIRMATION OF INTEGRITY
IN THE SUBMISSION AND HANDLING OF CLINICAL TRIALS RESEARCH DATA

1. I understand that the Aspirus Wausau Hospital Institutional Review Board (AWH-IRB) follows the Federal guidelines related to the reporting and submission of falsified data and other scientific misconduct, and will comply with those guidelines.

2. I recognize that the clinical research overseen by AWH IRB is critically dependent upon the trust of the American people. Submission of falsified data is scientifically abhorrent and cannot be tolerated, and it can destroy the public trust that is necessary for successful clinical research.

3. I recognize that the penalty for submission of falsified data by myself or by others from my Institution/Foundation may include: inability of myself or my Institution/Foundation to participate in future IRB approved activities.

4. If I observe, have knowledge of, or reasonably believe that falsification of patient records, data, or data analysis has occurred, I understand that AWH IRB policy requires that I report my observations, knowledge, or beliefs to the principal investigator or my supervisor at my Institution/Foundation and to the AWH IRB by contacting the Chief Medical Officer (CMO) at 715-847-2287.

   Any allegation(s) that misconduct has occurred may either be in writing or verbally. Written allegations shall be signed and dated. Both written and verbal allegations must identify the person(s) accused of misconduct and must adequately describe the nature of the alleged misconduct and evidence supporting the allegation. Anonymous allegations must be in writing.

   Allegations accusing a principal investigator at any Institution/Foundation of misconduct should be reported to the AWH IRB by contacting the CMO at 715-847-2287.

_____ _____
Name – PLEASE PRINT Signature

_____ _____
Institution/Foundation – PLEASE PRINT Date

Please return this form to: Attn: Lori Scheller, BS, CCRP
Institutional Review Board Coordinator
Aspirus Wausau Hospital IRB Office
333 Pine Ridge Boulevard
Wausau, WI 54401

Aspirus Wausau Hospital Institutional Review Board

Investigator's/Research Coordinator's Conflict of Interest Statement

The purpose of this form is to identify any Significant Financial or Significant Non-Financial Interest your or your Immediate Family members hold that have the potential to affect the conduct of studies you are involved with.
"Immediate Family" means spouse, dependent children, and/or other persons living in your household.
"Financial Interest Related to Research" means financial interest in sponsor, product, or service being tested, or competitor of the sponsor.

Investigator's/Coordinator's Name: _____ SS#_____
(please print) (optional)

Department: _____

Contact number _____ E-mail address _____

Do you or your Immediate Family have any of the following? (Check all that apply)

Involvement of you or your Immediate Family in the design of the research. Describe any steps planned to prevent the interest from interfering with the protection of subjects or from compromising one's professional judgment in conducting the study or reporting research results.

Ownership interest, stock options, or other financial interest related to the research unless it meets EACH of the following four tests:

- **Less than $10,000 when aggregated for you or your Immediate Family**
- **Publicly traded on a stock exchange**
- **Value will not be affected by the outcome of the research**
- **Less than 5% interest in any one single entity**

Compensation related to the research unless it meets EACH of the following two tests:

- **Less than $10,000 in the past year when aggregated for you and your Immediate Family**
- **Amount will not be affected by the outcome of the research**

Proprietary interest related to research including, but not limited to, a patent, trademark, copyright or licensing agreement.

Board or executive relationship related to research, regardless of compensation

Any other reason for which you believe you cannot provide independent review (for example: Substantial personal gifts from the sponsor).

If you checked any of the above, you are considered to have significant financial interest or significant Non-Financial Interest in one or more of the research projects you are involved with. Please disclose details of interests checked above and attach to this form.

OR

To the best of my knowledge, neither my Immediate Family, nor I have a relationship with or any significant financial or significant non-financial interest(s), directly or indirectly, with the sponsor of research that I am involved with.

I certify that, to the best of my knowledge, the above information is correct and that I have reviewed the Aspirus Wausau Hospital IRB Policy on Conflict of Interest in Human Subject Research (Onbase #5737) and hereby make the above disclosure(s) in accordance with such policy with regards to studies that I am involved with.

I further agree that in the event at any future date I have acquired a financial or non-financial interest in any business or organization that requires disclosure, I will promptly disclose such interest by further informing the Institutional Review Board at Aspirus Wausau Hospital.

Signature: _____ Date: _____

Aspirus Wausau Hospital
Supplemental Research Activity Form

Name:_____ Date:_____

Email Address (for updates in policy): _____

Number and Type of Studies Completed/Ongoing:

Certifications (check all that apply)*:

	Certification	Certifying Agency
□	CPI (Certified Physician Investigator)	Academy of Pharmaceutical Physicians and Investigators (APPI)
□	CTI (Certified Clinical Trials Investigator)	Association of Clinical Research Professionals (ACRP)
□	CCRA (Certified Clinical Research Associate)	Association of Clinical Research Professionals (ACRP)
□	CCRC (Certified Clinical Research Coordinator)	Association of Clinical Research Professionals (ACRP)
□	CIM (Certified IRB Manager)	National Association of IRB Managers (NAIM)
□	CIP (Certified IRB Professional)	Public Responsibility in Medicine and Research (PRIM&R)
□	Other (Specify):	Other (Specify):
If Certified, please attach the most current certificate		
***If not certified,** please attach documentation of Human Subject Protection training.		

Potential Conflict of Interest Disclosure:

	Yes*	No
Do you have a significant equity interest in any pharmaceutical/device/biotech company? Significant equity interest is defined as any ownership interest, stock options, or other financial interest whose value cannot be readily determined through reference to public prices (generally, interests in a nonpublicly traded corporation), or any equity interest in a publicly traded corporation that exceeds $50,000.		
Do you have a proprietary interest in any medical product being tested or marketed? Proprietary interest is defined as property or other financial interest in the product including, but not limited to, a patent, trademark, copyright or licensing agreement.		
Do you receive payments or other remuneration (e.g. equipment) from any pharmaceutical/device/biotech company (outside of payments for clinical studies) for consultation, honoraria, speaking, unrestricted research grants etc?		
Does any of the above apply to your immediate family (parents, children or grandchildren)?		
* ATTACH A DETAILED EXPLAINATION OF ANY 'YES' ANSWER TO THIS FORM WHICH INCLUDES 1) THE SPONSOR; 2) NATURE/AMOUNT OF THE INTEREST AND 3) STEPS TAKEN TO MINIMIZE THE POTENTIAL FOR BIAS. THIS INFORMATION WILL NOT BE DISCLOSED BEYOND THE IRB.		

Regulatory History:

	Yes*	No
Have you ever been audited by the FDA, OHRP or other research authority?		
Have you ever received a Form 483 from the FDA?		
Have you ever been named in an FDA Warning Letter or OHRP Determination Letter?		
Have you ever been Debarred/Disqualified/Restricted etc. by the FDA?		
* ATTACH A DETAILED EXPLAINATION OF ANY 'YES' ANSWER TO THIS FORM		

Commitments: (Note: These contain **modified and additional** elements than those found on the FDA Form 1572)

I agree to conduct the study (ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights and welfare of subjects

I agree to personally conduct or supervise the described investigation(s).

I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.

I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s).

I have read and understand the information in the investigator's brochure or other relevant literature, including the potential risks and side effects of the investigational product.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study (ies) are informed about their obligations in meeting the above commitments.

I agree to maintain adequate and accurate records in accordance with federal regulations and to make those records available for inspection.

I will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in federal/state/local regulations as well as institutional policies/procedures/instructions.

I agree to engage in the proper billing for research procedures, to not engage in the practice of offering referral fees or accept incentives from the sponsor tied to the number or rate of enrollment.

Principle Investigator Signature:_____
Date:_____

For Office Use Only

- □ Certification/CITI certificate Attached
- □ Regulatory History Review
- □ Conflict of Interest Review
- □ Signed/Dated
- □ FDA Debarment Scan
- □ FDA Disqualification Scan
- □ FDA Assurance Scan
- □ FDA Restriction Scan

Signature of Reviewing Staff:_____ Date Reviewed:_____

Aspirus Wausau Hospital
Institutional Review Board

Investigator/Co-Investigator Information

Name: _____

Business Name: _____

Address: _____

Phone: _____Fax:_____

Title: _____

Contact Person's Name: _____**Phone:** _____

Education / Degrees: _____

Contents to be kept in investigator's file

- ❑ Investigator Agreement
- ❑ Affirmation of Integrity in the Submission & Handling of Clinical Trials Research Data
- ❑ Documentation of Education Received (to be collected annually)
- ❑ Investigator's Financial Disclosure Form (to be collected annually)
- ❑ Supplemental Research Activity Form

Name of Studies where investigator serves as **Primary** Investigator:

Study Name: _____
Study Name: _____
Study Name: _____
Study Name: _____
Study Name: _____
Study Name: _____
Study Name: _____
Study Name: _____
Study Name: _____
Study Name: _____
Study Name: _____

Name of Studies where investigator serves as Co-Investigator

Study Name: _____
Study Name: _____
Study Name: _____
Study Name: _____
Study Name: _____
Study Name: _____

Aspirus Wausau Hospital
Institutional Review Board

Educational Requirement - Resources

Human subject research investigators, co-investigators, coordinators and Institutional Review Board (IRB) members and staff are required to complete appropriate education and training before reviewing or conducting human subject research. Documentation of such training must be submitted to the IRB prior to conducting human subject research. Documentation of continuing education (3 hours of continuing education programs or a 1-hour computer based training module per year) regarding human subject research must be provided to the IRB on an annual basis.

Methods that may be used to obtain this continuing education will include: 1) internal or external seminars on human subject protection topics, 2) videotapes on human subject protection issues, 3) computer-based educational modules regarding human research protection (a list of examples is noted below), and 4) other educational programs as deemed appropriate by the Wausau Hospital IRB.

http://cme.cancer.gov/clinicaltrials/learning/humanparticipant-protections.asp

This free, web-based course presents information about the rights and welfare of human participants in research. The two-hour tutorial is designed for those involved in conducting research involving human participants. It satisfies the NIH human subjects training requirement for obtaining Federal Funds. You will have the option of printing a certificate of completion from your computer upon completing the course.

http://ohsr.od.nih.gov (Office of Human Subjects Research, National Institutes of Health, Computer Based Training (CBT). Completion of this Computer-Based Training (CBT) course is an educational requirement for all researchers in NIH's Intramural Research Program (IRP), and other NIH employees who conduct or support research involving human subjects along with IRB members. A certificate can be printed upon completion.)

TAB 2: AWH IRB Policies & Procedures for Research

(see individual policy listed on CD or access AWH intranet Onbase)

POLICIES:

Title	Onbase Number
Protection of Human Subjects in Research Policy & Procedure……..	#4966
Review of Communications Regarding Research …….	#5314
Clinical Research Conflict of Interest (COI) Policy…….	#5737
Compensation for Identifying, Enrolling, or Referrals……	#10314
Handling Allegations of Non-Compliance in Research…….	#10315
Scientific Misconduct Policy……	#5738

STANDARD OPERATING PROCEDURES (SOPs):

Title	Onbase Number
Review of Exempt Projects……..……..	#6649
Emergency Use Review Process……..	#6650
Expanded Access Review……..	#12229
Review of Humanitarian Use Devices…….	#6654
Expedited Review……	#6791
Initial Review Process-Criteria for IRB Approval……	#6658
Continuing Review and Renewal Process……..	#6744
Adverse Event and/or Unanticipated Problem Reporting…….	#6653
Deviation & Protocol Exceptions……..	#10313
Reviews Requiring Special Considerations-Vulnerable Populations..	#7495
Informed Consent for Research Subjects……	#6660
Informed Consent for Non-English Speaking Research Subjects…..	#12061
Human Subject Protection Education & Training Policy & Procedure..	#6652
IRB Membership……	#6651
IRB Administration…….	#6655
IRB Meeting Operations……	#6657
IRB Signatory Authority……	#7253
Research Investigator(s) & Supporting Research Staff Requirements..	#6656
IRB Fees……..	#12013

ASPIRUS, INC. Policy

Title	Onbase Number
Use & Disclosure of Protected Health Information (PHI) for Research Purposes……..……..	#6572
Corporate Ethics Policy-Conflict of Interest…….	#2348

Access Policies & Procedures on Aspirus Intranet:
http://aspirusintranet/index.php?option=com_content&view=article&id=27&Itemid=57

TAB 3: Investigator & Research Staff Responsibilities

(AWH & Guidance for Industry Investigator Responsibilities: Protecting the Rights, Safety, and Welfare of Study Subjects PI Responsibilities)

ASPIRUS WAUSAU HOSPITAL, INC.
Passion for excellence. Compassion for people.

ONBASE POLICY ID: #6656
POLICY STATUS: FINAL
EFFECTIVE DATE: 4/20/10
REVISION DATE:

P&P REF # 01-01-138
REPLACES:
DOCUMENT TYPE: Policy
PROPOSED BY: IRB
RESPONSIBLE DEPT: IRB

VERSION HISTORY: 1/25/05, 12/2/03
APPROVALS:
Committee/Dept. Approval and Dates: IRB 05/15/07, 04/20/10 AWH Board of Directors 07/23/07, May 2010

SUBJECT: RESEARCH INVESTIGATOR(S) AND SUPPORTING RESEARCH STAFF REQUIREMENTS & RESPONSIBILITIES

PURPOSE:
To outline the requirements and responsibilities of research investigators and supporting research staff in carrying out research studies under the auspices of the Aspirus Wausau Hospital's Institutional Review Board (AWH-IRB).

Each individual involved in a research study is responsible for complying with applicable laws, regulations, and the Institutional Review Board Policies and Procedures, including Investigators, Co-investigators, and Supporting Research Staff. Investigators are responsible for the overall conduct and supervision of research studies and therefore must have the necessary skills and expertise to perform all procedures involved in the research study. Investigators must also ensure that all co-investigators and research staff are carefully chosen for their expertise and expected involvement in the research study.

AREAS AFFECTED/STAKEHOLDERS:
Any entity whose research falls under the auspices of the AWH-IRB
Institutional Review Board (IRB)
Investigators
Research Coordinators and Research Staff

DEFINITIONS:
Investigators: All physicians, practitioners, or staff who are responsible for the overall design, conduct, supervision, and reporting of research data, including principal investigators and co-investigators.

Research Coordinators: All personnel who directly support the investigator in the design, conduct and reporting of research.

Research Staff: Personnel who assist the research coordinators in carrying out research studies.

POLICY:
I. COMPLIANCE WITH IRB POLICIES AND APPLICABLE LAWS

A. Applicable Food and Drug Administration (FDA), Department of Health and Human Services (DHHS) regulations, and the IRB Policies and Procedures require each

individual involved in conducting a research study to:

1. Conduct the research study in accordance with all applicable FDA regulations (including 21 CFR Parts 50, 56, 312, 812 and 814), DHHS regulations (including 45 CFR Parts 46, 160, and 164), the Belmont Report, and any other conditions of approval as determined by the IRB.
    a. Ensure that a clinical investigation is conduced according to the signed investigator statement for clinical investigations of drugs, including biological products or agreement for clinical investigations of medical devices, the investigational plan and applicable regulations
    b. Protect the rights, safety and welfare of subjects under the investigator's care
    c. Control drugs, biological products, and devices under investigation (21 CFR 312.60. 21 CFR 812.100)

(See also Guidance for Industry – Investigator Responsibilities – Protecting the Rights, Safety, and Welfare of Study Subjects from DHHS-FDA dated Oct. 2009)

2. Conduct the research study in accordance with IRB policies and procedures, including the following:Protection of Human Subjects in Research Policy (Onbase #4966)), IRB Standard Operating Procedures, the Scientific Misconduct Policy (#5738), the Clinical Research Conflict of Interest Policy (#5737), the Communications Regarding Research Policy (#5314), and the Use and Disclosure of PHI for Research Purposes Policy (#6572).

3. Conduct the research study in accordance with the research study investigational plan and/or protocols.

4. Understand and have a working knowledge of the research study.

5. Take all measurements to protect the rights, safety, and welfare of subjects participating in the research study.

II. INVESTIGATOR RESPONSIBILITIES

A. Investigators have the following responsibilities when conducting research studies:

1. Procedures and interventions included in a study are to be consistent with the principal investigator's scope of practice. The IRB will investigate and make the final determination for approval when a concern arises regarding study procedures and the investigator's scope of practice.

2. Active investigators will be required to complete the following forms for the IRB prior to conducting human subject research. Furthermore, certain forms will also be completed and submitted on an annual basis. The Human Research Protections Coordinator sends the forms to investigators for completion and tracks the completed documents. The forms are filed in the investigator's IRB file.

    a. Investigator Agreement form (Appendix A) (initial completion)
    b. Affirmation of Integrity in the Submission and Handling of Clinical Trials Research Data form (See Policy #5738) (initial completion)
    c. Annual Financial Conflict of Interest form (See Policy #5737) (initial and annual completion)

d. Human Subject Protection Education and the Education Documentation Table (See SOP #6652) (initial and annual completion).
e. Resume or CV (initial submission)

B. Investigators have the following responsibilities in submitting research study information to the IRB:

1. Initial Approval and Continuing Review of the study: The investigator must submit a research study to the IRB for approval before beginning the research study. If the research study is approved, the investigator must submit to the IRB any and all continuing review materials, including progress reports, as required by the IRB (See SOP #6658 and #6744).

2. Changes in Research and Serious Adverse Events: The investigator must submit any changes in the research study or the informed consent form to the IRB prior to implementation. The investigator must report to the IRB any serious adverse events occurring in research studies approved by the IRB (See SOP #6653).

3. Closure, Completion or Termination: The investigator must submit to the IRB any information regarding the closure, completion, or termination of a research study, including requests for final closure. For final closure of a study, the investigator must submit a progress report that includes when the study was initially approved, the total number of subjects enrolled, any serious adverse events not previously reported, any new findings, and any subject withdrawals.

4. Addition or Deletion of Investigators: The investigator must report to the IRB any changes, including additions and deletions, in the principal and co-investigators of a study.

5. Final Report: The investigator will submit to the IRB a final report after the closure of a research study. This report will be reviewed by the IRB for information only.

III. RESEARCH COORDINATOR AND RESEARCH STAFF RESPONSIBILITIES

A. Research coordinators will be required to complete the following forms for the IRB prior to conducting human subject research. Furthermore, certain forms will also be completed and submitted on an annual basis. The Human Research Protections Coordinator sends the forms to the research coordinators for completion and tracks the completed documents. The forms are filed in the coordinator's IRB file.

1. Affirmation of Integrity in the Submission and Handling of Clinical Trials Research Data form (See Policy #5314) (initial completion)

2. Annual Financial Conflict of Interest form (See Policy #5737) (initial and annual completion)

3. Human Subject Protection Education and the Education Documentation Table (See SOP #6652) (initial and annual completion).

B. Research staff will be required to complete Human Subject Protection Education and the Education Documentation Table before conducting human subject

research and on an annual basis. The IRB Coordinator sends the forms to the research staff for completion and tracks the completed documents. The forms are filed in the research staff's IRB file.

C. Complete any additional training/licensing requirements to perform study-related duties.

REFERENCES:

21 CFR 50, Protection of Human Subjects, FDA.

21 CFR 56, Institutional Review Boards, FDA.

21 CFR 812, Investigational Device Exemptions, FDA.

45 CFR 46, Protection of Human Subjects, DHHS.

45 CFR 160, Standards for Privacy of Individually Identifiable Health Information, DHHS.

45 CFR 164, Standards for Privacy of Individually Identifiable Health Information, DHHS.
The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, "The Belmont Report," April 18, 1979.

Oct. 2009 DHHS-FDA: Guidance for Industry- Investigator Responsibilities: Protecting the Rights, Safety, and Welfare of Study Subjects.

AUTHOR(S):

Lori Scheller
Institutional Review Board
7/23/3007, rev. 4/20/2010
NKZ-P

TAB 4: Ethics Of Human Subject Research

Nuremberg Code

Declaration of Helsinki

Belmont Report

The 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.]

http://www.hhs.gov/ohrp/references/nurcode.htm

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. 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 not be applied without consideration of all other relevant paragraphs.
2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.
3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
4. 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."
5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.
6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.
7. 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 current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.
10. Physicians should 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.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. 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.
13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.
14. The design and performance of each research study involving human subjects must be clearly described 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, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.
15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. 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 change to the protocol may be made without consideration and approval by the committee.
16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy DoH/Oct2008 3 volunteers require the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.
17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.
19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.
20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.
21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.
22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.
24. In medical research involving competent human subjects, 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, 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. DoH/Oct2008 4
25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.
26. When seeking informed consent for participation in a research study the physician should 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 should be sought by an appropriately qualified individual who is completely independent of this relationship.
27. For a potential research subject who is incompetent, 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 population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.
28. When a potential research subject who is deemed incompetent 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.
29. 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 population. In such circumstances the physician should 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 should be obtained as soon as possible from the subject or a legally authorized representative.
30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors 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. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.
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C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research 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.

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

• The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or

• Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the 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 interfere with the patient-physician relationship.

35. In the treatment of a patient, where proven interventions do not exist or 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. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

BELMONT REPORT

THE BELMONT REPORT ETHICAL PRINCIPLES AND GUIDELINES FOR THE PROTECTION OF HUMAN SUBJECTS OF RESEARCH

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research April 18, 1979

SUMMARY: On July 12, 1974, the National Research Act (Pub. L. 93-348) was signed into law, there-by creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. One of the charges to the Commission was to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and to develop guidelines, which should be followed to assure that such research is conducted in accordance with those principles. In carrying out the above, the Commission was directed to consider: **(i)** the boundaries between biomedical and behavioral research and the accepted and routine practice of medicine, **(ii)** the role of assessment of risk-benefit criteria in the determination of the appropriateness of research involving human subjects, **(iii)** appropriate guidelines for the selection of human subjects for participation in such research and **(iv)** the nature and definition of informed consent in various research settings. The Belmont Report attempts to summarize the basic ethical principles identified by the Commission in the course of its deliberations. It is the outgrowth of an intensive four-day period of discussions that were held in February 1976 at the Smithsonian Institution's Belmont Conference Center supplemented by the monthly deliberations of the Commission that were held over a period of nearly four years. It is a statement of basic ethical principles and guidelines that should assist in resolving the ethical problems that surround the conduct of research with human subjects. By publishing the Report in the Federal Register, and providing reprints upon request, the Secretary intends that it may be made readily available to scientists, members of Institutional Review Boards, and Federal employees. The two-volume Appendix, containing the lengthy reports of experts and specialists who assisted the Commission in fulfilling this part of its charge, is available as DHEW Publication No. (OS) 78-0013 and No. (OS) 78-0014, for sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402. Unlike most other reports of the Commission, the Belmont Report does not make specific recommendations for administrative action by the Secretary of Health, Education, and Welfare. Rather, the Commission recommended that the Belmont Report be adopted in its entirety, as a statement of the Department's policy.

NATIONAL COMMISSION FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL AND BEHAVIORAL RESEARCH MEMBERS OF THE COMMISSION

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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 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 to 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 entitle. **2. Assessment of Risks and Benefits.** -- The assessment of risks and benefits requires a careful arrayal 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 occasion 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.