

<b>TITLE</b>	Formation and Operation of an Institutional Review Board	
<b>NUMBER</b>	TRw-MS-504	May 08
<b>JCAHO FUNCTIONS</b>	RI, IM	
<b>APPLIES TO</b>	Novant Health Triad Region (excluding TMC)	

**I. SCOPE / PURPOSE**

- A The responsibility for evaluating "research involving human subjects" has been assigned to Institutional Review Board (IRBs) by the Food and Drug Administration (FDA) (Title 21, CFR 56), and the Department of Health and Human Services (DHHS) (Title 45, CFR 46). Federal regulations define research as "generalizable information" and allow for the IRB to decide exemption from IRB review. Hence, it is expected that all research involving human subjects with the intended purpose of gathering information in a systematic manner be required to submit the proposal for IRB review. "Research" designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to contribute to generalizable knowledge
  
- B. To describe the processes and procedures for forming and managing a duly-constituted Institutional Review Board (IRB) within Forsyth Medical Center to review and monitor proposals for research involving human subjects that are to be conducted by clinical investigators, medical or nursing staff, doctorate professionals, and students in accredited health science programs under the sponsorship of Forsyth Medical Center or by other organizations or individuals for which the IRB has agreed to assume supervisory responsibility. Forsyth Medical Center’s IRB is an administrative body established to protect the rights and welfare of human research subjects recruited to participate in research activities conducted under the auspices of Novant Health Triad Region. Forsyth Medical Center IRB reserves the right and assumes the responsibility, under its Federalwide Assurance to review and approve all research carried out in any of its facilities to that end in its mandate to protect the rights and safety of human subjects in research, the IRB will carry out this evaluation subject to the ethical principals contained in the *Belmont Report* namely: with respect to persons, beneficence and justice.
  
- C. To provide a reference for administration, the IRB, investigators, sponsors, students, the community and others involved in research on the methods of operations and standards for Forsyth Medical Center IRB.

**II. QUALIFIED PERSONNEL**

IRB Chair, IRB Members, IRB Manager, Investigators, Clinical Research Personnel

**III. EQUIPMENT**

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**V. PROCEDURE**

**A. IRB Composition**

1. The Forsyth Medical Center IRB shall consist of voting and non-voting members.
2. The IRB voting members will be an odd number of members with a minimum of five (5) and no more than fifteen (15) voting members sufficiently qualified to carry out the IRB's stated purpose
3. Members will be from a variety of backgrounds, qualified through experience and expertise, diversity (consideration of gender, race, cultural background) and sensitivity to community attitudes. One member may satisfy more than one membership category. The IRB will include at least one voting member whose primary concerns are in scientific areas; at least one member whose primary concerns are in non-scientific areas; and at least one member who represents the community-at-large.
4. The community member(s) shall not be personally affiliated with the institution and shall not have an immediate relative affiliated with the institution
5. Members will be selected on the basis of maturity, experience and expertise and will be recommended for appointment by the IRB Chair and approved by the Medical Staff Executive Committee and Board of Trustees
6. The IRB may invite individuals with particular expertise or competence in specific areas to assist in review of complex issues as needed and these individuals will not participate in the voting process. Such individuals will not function as voting, non-voting or alternate members. The involvement of individuals other than the IRB may be represented by a written document or by presentation to the IRB. The individual may be invited to participate in a limited portion of a meeting. The individual may be asked to provide Curriculum Vitae for an attachment to the minutes.
7. The board may appoint a Vice-Chair to serve in the absence of the Chairperson who will have the full authority and responsibility assigned to the Chairperson. He will possess qualifications similar to the Chairperson.
8. A roster of IRB members identified by name, earned degrees, and representative capacity, sufficient to describe each member's chief contribution to the IRB will be maintained. The roster will be distributed to all IRB Members and to Investigator's and Sponsors as needed

**B. Term of Appointment**

1. All members shall be appointed to serve a minimum of 1 year with automatic yearly re-appointment unless otherwise specified by the IRB member.
2. In the event of the resignation or death of a member, the Chairperson of the IRB will appoint an interim replacement to serve the remaining portion of the resigning/deceased member's term if the term is less than one-year
3. The Chairperson shall be elected by the IRB membership and approved by the Medical Staff Executive Committee. The Chairperson will serve a minimum of two years with automatic re-appointment to consecutive terms at the discretion of the Medical Staff Executive Committee and Board of Trustees.

**C. Duties and Responsibilities of the IRB**

**1. Board**

- a) The IRB will meet monthly on the first Thursday of each month or other day determined by the chairperson and review research proposals and actions submitted for review by the application due date for each month as published in the current Investigator's Manual.
- b) All Members (Voting and Non-Voting) are expected to attend all meetings unless otherwise excused.
- c) If a member fails to attend 50% of the scheduled meetings within a 12-month period, the member may be removed at the IRB's discretion.

- d) IRB members will serve without remuneration.
- e) IRB members are covered under the institution's Health Director and Officer's Liability coverage.
- f) Members must be in attendance to vote. Members may not vote in a decision/action in which they have a vested interest in the project and may be asked to not participate in the discussion and/or be dismissed from the meeting when protocol is being discussed.
- g) Non-voting members will not participate in the voting process.

**2. Chairperson/Vice-Chair**

- a) The Chairperson or Vice-Chair is responsible for chairing the meetings, conducting business in a manner to ensure that each proposal is fairly and completely reviewed, seeing that the IRB reaches a decision on the disposition of each proposal and communicating these decisions to the individual(s) who submitted the proposal.
- b) The Chairperson directs the IRB to ensure that it is operating in accordance to its policies and procedures and within compliance of all federal and state regulations.
- c) The Chairperson will submit the minutes to the IRB for approval.
- d) The Chairperson shares in the responsibility of ensuring that new members receive adequate orientation prior to being appointed to the IRB. The orientation / training includes reviewing of FDA/OHRP reference manual, Forsyth Medical Center IRB policy and procedure manual, review of sample protocols, informed consent template, approved minutes for previous year, and other educational materials as they become available. Currently, IRB members have access to the online CITI program. All new members will complete the CITI program (or equivalent program as determined by the IRB manager) within one month of their appointment or as determined by the Chairman.
- e) The Chairperson will review the IRB Policy and Procedure manual annually and make recommendations to the IRB for necessary revisions or updates. The minutes will reflect this review.

**D. Operations**

**1. Administration**

- a) Administration of the IRB shall include managing all operational issues to support the IRB and Chairperson; securing adequate budget allocation, securing adequate resources (meeting area, filing space, reproduction equipment and computer access), and providing oversight and direction for the IRB to operate within institutional, federal and state guidelines.
- b) The decision of Forsyth Medical Center IRB is independent, however reciprocity of the approval process of a Forsyth Medical Center IRB can be extended to another IRB if requested and approved by both IRB's.
- c) The IRB Manager will be responsible for providing educational information to the IRB and alerting the IRB to changes in regulations, policies and procedures from the institution and federal agencies.
- d) Fees will be charged for industry sponsored research protocols. The fee schedule will be determined by Novant Health Triad Region administration and Principal Investigators will be responsible for remittance. Payment of fee is not dependent on the pharmaceutical company's agreement, but is the Principal Investigator's responsibility.
- e) Protocols that are not funded can request a waiver of fee. These include

student or original research, collaborative group protocols and federally funded projects. Waiver will be granted at the Chairperson/Vice-Chairs discretion.

- f) The IRB will maintain a local office staffed by an IRB Manager, and other support staff as deemed necessary to perform the required functions of the IRB Office.
- g) The Manager (and other support staff as deemed necessary to perform the required functions of the IRB Office) will maintain files of the Policies and Procedures, Regulatory Operating Guidelines, meeting agendas, meeting minutes and all communications with IRB members.
- h) The IRB Manager and other support staff as deemed necessary to perform the required functions of the IRB Office will maintain records in accordance with Novant record retention policy for each proposal submitted to the IRB. These records will include, but may not be limited to:
  - (1) The original research Proposal and amendments;
  - (2) Copies of the IRB's actions and decisions signed by the Chairperson and/or Alternate;
  - (3) Records of periodic Proposal renewal;
  - (4) A current Investigator's Brochure;
  - (5) All regulatory documents including valid Form 1572; Investigator's Curriculum Vitae, Investigator's Summary;
  - (6) Adverse event reports;
  - (7) Continuing Review reports, final study report and closure.
- i) The IRB Manager, (and other support staff as deemed necessary to perform the required functions of the IRB Office) will be responsible for maintaining separate files for each study, minute records, documentation of the IRB's decisions and all other appropriate action and other documents to demonstrate compliance with applicable regulations. All documents will remain confidential and not available for review outside of the IRB, the Investigator and/or other authorized staff including FDA, OHRP or Forsyth Medical Center administration.
- j) Formal minutes will be prepared by the IRB Manager and reported in a timely manner for approval by the IRB. Minutes will include a list of members present, a record of discussion issues, a record of IRB decisions and a record of voting. Minutes will be reviewed and approved by the IRB in a timely manner, signed by the Chairperson and maintained in the IRB office.
- k) The IRB Manager may maintain an electronic database with records of all IRB actions.
- l) All IRB files will be made available for inspection by duly authorized representatives of federal or state government or of the Institution.
- m) Files will be maintained in confidential manner, locked, and stored independent of other institutional files.
- n) A current roster of IRB members will be maintained and available upon request.
- o) All records related to research proposals will be retained for at least three (3) years after the research project is completed or terminated.
- p) The IRB Manager will be responsible for conducting audits of records to meet regulatory and institutional guidelines and/or as requested by the Chairperson, IRB or administration. Findings will be summarized and reported to the Chairperson and the IRB.

## 2. Meetings

- a) Meetings will be held monthly with the yearly schedule posted prior to the beginning of the calendar year.
- b) Ad hoc meetings may be called by the Chairperson as deemed necessary to facilitate review of Proposals, address policies and procedures or to discuss the need for immediate action to protect the rights or safety of human subjects.
- c) Announcement of an upcoming meeting will be sent at least one week prior to the scheduled meeting time.
- d) All members will receive the following documents in preparation of the meeting: Agenda, New Study Applications including the Study Summary, Informed Consent document, and other items requiring IRB actions
- e) The Chairperson may elect to delegate primary review of selected protocols to other Members with sufficient scientific qualifications to review such research. Primary reviewers will receive all submitted materials for review and will document their recommendations for review by the full board.
- f) The current FDA approved 'Protocol' and 'Investigator's Brochure' will be available at the meeting for review by the IRB at the time the study is presented. Revisions to the protocol and amendments to the Investigator's Brochure will also be available to the IRB and a revised informed consent document or a written summary of the consent changes will be reviewed by the IRB as required to reflect revisions and amendments.
- g) Meetings are considered 'open' in that interested physicians, researchers, staff, and/or others may attend the meeting provided they understand and agree to the confidentiality of the meeting. The Chairperson or any IRB Member may request the meeting to become 'closed' and whereby only IRB Members [Voting and Non-voting] members would be present. This may be applicable for any portion or all of a meeting.
- h) It is the responsibility of the Chairperson, to address the issue of confidentiality with anyone attending the meeting who is not an IRB member. The Chairperson may request to have the individual sign a Statement of Confidentiality prior to granting permission for the person to attend. This will be noted in the minutes and if there is a signed Statement of Confidentiality it will be recorded in the minutes as an amendment.
- i) A quorum is required to open a meeting. The presence of a simple majority (one more than 50% of the membership) will constitute a quorum. Actions are made by a simple majority of the members attending a meeting.
- j) At least one non-scientific member must be present as a part of the required quorum. An alternate member who is a non-scientific representative can be substituted in attendance.

**3. Voting**

- a) A member must be present at the meeting to participate in the voting process. Proxy votes are not accepted. A member may participate by teleconference if a truly interactive arrangement is provided. Meeting minutes will document the level of participation in such a setting.
- b) Voting is done by voice affirmation, with decisions made by a simple majority. A record of dissenting votes will be maintained.
- c) A member with a conflict of interest may be counted as present for the purpose of determining a quorum, but may not participate in the voting process for the proposal in which they have a vested interest in the

research, and thus may present a conflict of interest. In some cases, the member may be asked to exit the meeting room during the deliberation and voting procedure to minimize conflict of interest issues. In such a setting, quorum must be maintained for voting to take place.

**E. Criteria for IRB Approval**

1. Risks to subjects are minimized.
2. Risks to subjects are reasonable in relation to anticipated benefits.
3. Selection of subjects is equitable.
4. Informed consent is adequate, written such that patient can understand and outlines risks and benefits of participation in accordance with federal, state and institutional guidelines.
5. Informed consent is sought, obtained and appropriately documented per institutional policies and procedures.
6. Adequate provisions to protect the privacy of subjects and maintain confidentiality of data in compliance with current Federal and State guidelines including compliance with HIPAA regulations.
7. Appropriate safeguards are invoked in order to protect the rights and the welfare of the vulnerable including children.
8. Demonstration that the selection of participants is equitable.
9. Principal Investigator has appropriate credentials to conduct study.
10. Principal Investigator discloses to IRB whether study was presented to another IRB and was not approved.
11. IRB has been fully informed of the manner in which the study is to be conducted the researchers involved in the process and any conflicts of interest.
12. Approvals are valid for a specified period of time not to exceed a maximum of one (1) year.
13. The Principal Investigator has acknowledged [by signature] his/her awareness and agreement to comply with applicable federal, state and institutional policies and procedures pertinent to the research process and protection of human subjects.

**F. Research Proposal Submissions**

1. Research Proposal Summaries will be submitted to the IRB Manager on standard approved forms according to the schedule of submission deadlines published with the meeting schedule each year.
2. To be considered for review each initial proposal submission will contain all required documents for the applicable submission as described in the 'Investigator's Handbook' which include but are not limited to:
  - a fully complete protocol application packet
  - a complete and dated protocol,
  - one copy of the current Investigator's Brochure or Package Insert for the drug or device to be studied,
  - a concise description of the proposed study, explanation of the potential risks and benefits to the prospective study participant,
  - a proposed informed consent document, (an electronic copy should be submitted)
  - FDA Form FDA 1572 or Statement of Investigator [if applicable],
  - Curriculum vitae of Principal and Subinvestigator(s) which have been signed and dated within the last 2 years and
  - Current medical licenses for Principal and Subinvestigator (s).
  - A printed copy of each of these items with valid signature(s) as appropriate is required
  - Copy of Human Subjects Protection Research Education Certificate from a FMC IRB approved program.
  - A disc containing the informed consent or electronic copy and application file should be submitted for processing

3. A request for review of a Proposal that does not include all of the required documents must be explained in writing providing detail as to the basis for the item not being included. The Chairperson will determine if an incomplete Proposal submission may be presented to the IRB for review.
4. The IRB may establish criteria for the readability of the Informed Consent form, using its own selected method of calculation. The Informed Consent document should meet the institution's guidelines which are consistent with applicable regulations, Federal, State and Local. If there is a significant deviation from this standard, the proposal will not be submitted to the IRB until it is revised. If there are special circumstances that warrant non-compliance, a written request to the IRB for exception is required, whereby the Chairperson will present the request to the IRB for decision.
5. Case Report Forms may be omitted from the Proposal submission unless specifically requested by the IRB or if there is unusual information requested on the Form that would increase the risk to the patient with regards to confidentiality or otherwise.
6. Requests for renewal, revision, closure and termination will be submitted to the IRB in the manner outlined in the 'Investigator Handbook' using the approved forms.

**G. Protocol for IRB Review**

- 1) Submissions to the IRB using the Submission Application format will be received and reviewed for completeness by IRB Manager and prepared for the Chairperson
- 2) The Investigator may be contacted after submission and informed of any outstanding documents that need to be submitted. Administrative errors and omissions can be addressed at this time.
- 3) The IRB Chair or another member with sufficient scientific expertise of his choosing will receive all of the documents submitted to conduct "primary review" of the research proposal. He will document his findings and recommendations on the "Primary Reviewers Report and Recommendation (attached) and present these findings/recommendations to the board.
- 4) Submissions to the IRB will be transmitted by the IRB Manager to the IRB members in sufficient time before the scheduled meeting to allow thorough review of each Proposal. At a minimum, all IRB members will receive a study summary or continuing review report and a proposed informed consent form for each research proposal in sufficient time prior to the scheduled meeting to give adequate consideration. IRB members will have access to all necessary supporting information for each proposal.
- 5) At the IRB meeting the proposal should be presented by the Principal Investigator, sub-investigator, or other research personnel identified on Form 1572 or New Study Application Packet in sufficient detail to permit adequate consideration. Following this presentation, the proposal will be discussed until adequate information is available for a decision.
- 6) The IRB may request a review/opinion from one or more qualified outside experts.
- 7) Any IRB member with a conflicting interest in a proposal will identify this conflict and abstain from deliberations and voting on that proposal, except to provide information as requested by the IRB. Such abstentions will be recorded in the minutes.
- 8) By majority vote of the members present, the IRB may reach one of the following decisions regarding each proposal:
  - Approved as presented.
  - Approved, subject to specific modifications.
  - Disapproved.
  - Tabled/Deferred. Pending evaluation of additional requested information.

- 9) If the IRB approves a proposal subject to modifications, the IRB must specify, by majority vote of the members present, whether the changes will require full IRB approval or may be approved by the Chairperson on behalf of the IRB.
- 10) The IRB will determine at the time of initial approval of a proposal by majority vote, the required review interval for each research project. This will be determined by the level of risk and complexity of the protocol and other factors under the IRB's purview. This will be recorded in the meeting minutes and communicated to the Investigator in the letter of approval when applicable.
- 11) A summary of the IRB's discussions and a record of its decisions, including but not limited to the final disposition of each Proposal, will be prepared by the IRB Manager, or IRB staff and submitted to the Principal Investigator. The Chairperson will notify in writing, the Principal Investigator informing him/her of its decision to approve, disapprove, table or modify a proposal. The Principal Investigator also will be notified of the duration of the IRB's approval, which in no case will exceed one year. The decisions of the IRB will be included in the proposal files maintained by the IRB Manager.
- 12) If the proposal is not approved, the investigator has the option of either accepting the disapproval, modifying and resubmitting, or appearing before the IRB for reconsideration. If a proposal is disapproved, reasons for such disapproval will be documented. If a proposal requires modification, the items of concern will be detailed to assist the Investigator.
- 13) The Principal Investigator may appeal disapproval within 30 days of receipt of the notice of disapproval. Such a written appeal must be forwarded to the IRB Chair for consideration. If an appeal is made, the item will be placed on the next meeting agenda and reviewed by the full IRB. The Principal Investigator will be notified of a decision on the appeal within 60 days.
- 14) An appeal may be resolved only by full IRB review. In no case may an external body or official override the decision of Forsyth Medical Center IRB.
- 15) A copy of the stamped valid informed consent document that is to be used for all participants will be included in notifications of approval. FMC IRB does not re-stamp a consent form annually, at the time of continuing review- approval. Forsyth Medical Center Institutional Review Board stamps an approved date on the consent at the time of the respective approval. This approval date stamp is valid for the version of the consent form that was approved (either initial review or a revision that occurred subsequent to that original approval). At the time of annual continuing review, the IRB verifies the use of the most recently approved consent form.
- 16) Studies are approved for periods from 3 - 12 months at the IRB's discretion to ensure adequate oversight and protection of human subjects. No study may be approved for longer than a 12-month period without review and application for renewal. The investigator will be notified of the duration of approval when the research is initially approved.
- 17) The use of media, or advertising, for study announcement and/or recruitment purposes requires prior IRB approval. Advertising for research subjects is not in and of itself an objectionable practice. However, the IRB should review the information contained in the advertisement, and the mode of its communication, to determine that the procedure for recruiting subjects affords adequate protection. Advertising includes printed materials, radio, television, web site and/or phone solicitation. The text must be submitted to the IRB with its exact copy and illustration (if any) together with details regarding the method of distribution and target audience. The Principal Investigator will submit the written request to the IRB office by the monthly submission deadline for inclusion on the monthly agenda. Ads must comply with the context standards described in the federal regulations and those of the IRB. (FDA - 21 CFR 312.7(a) and 21 CFR 812.7(d)).

- 18) Advertisements used to recruit subjects should be seen as an extension of the informed consent and subject selection processes. The IRB is responsible for securing that appropriate safeguards exist to protect the rights and welfare of research subjects (FDA 21 CFR 56.111(b)).
- 19) Communication between professional staff regarding a study for the purpose of informing peers rather than recruiting is not considered advertisement and therefore does not require IRB approval.
- 20) Participants may be paid for their participation in research. In such cases the IRB should review both the amount of payment and the proposed method of disbursement to assure that neither present problems of coercion or undue influence. All information concerning payment including the amount and schedule of payment must be set forth in the informed consent document.

**H. IRB Review of Medical Devices**

1) Description

The procedures for Institutional Review Board (IRB) review of significant risk (SR) and non-significant risk (NSR) investigational device use  
 Unless exempt from the Investigational Device Exemption (IDE) regulations, an investigational device must be categorized as either "significant risk" (SR) or "nonsignificant risk" (NSR). The sponsor makes the initial recommendation that a device presents a nonsignificant or significant risk. The principal investigator (PI) submits the proposed study to a convened IRB for SR and NSR studies for formal determination of the appropriate SR/NSR category.

Device Class Description

- a) Class I: General controls: crutches, band aids
- b) Class II: Special control: wheelchairs, tampons
- c) Class III: PreMarket Approval: heart valves (known to present hazards requiring clinical demonstration of safety and effectiveness) - OR - not enough known about safety or effectiveness to assign to Class I or II

2) Definitions

- a) A medical device is defined as any health care product that does not achieve its primary intended purposes by chemical action or by being metabolized.
- b) An investigational device is a medical device which is the subject of a clinical study designed to evaluate the effectiveness and/or safety of the device.
- c) A significant risk device study is a study of a device that presents a potential for serious risk to the health, safety, or welfare of a participant and
  - (1) is intended as an implant; or
  - (2) is used in supporting or sustaining human life; or
  - (3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or
  - (4) otherwise presents a potential for serious risk to the health, safety, or welfare of a participant.
- d) A nonsignificant risk device study is one that does not meet the definition for an SR study. A study is considered NSR if it
  - (1) is noninvasive;
  - (2) does not require an invasive sampling procedure that presents significant risk;
  - (3) does not by design or intention introduce energy into a subject; and
  - (4) is not used as a diagnostic procedure without confirmation of the diagnosis by another medically established diagnostic product or procedure.

- e) A claim that the device is exempt from the IDE requirements of the Food and Drug Administration (FDA) must reference the exemption category being claimed; it is the sponsor's responsibility to provide sufficient justification to support the exemption category. An exemption from the IDE requirement is not an exemption from the requirement for prospective IRB review or informed consent.
- 3) Procedure for Device Review
- a) The PI includes in the IRB application the sponsor's initial assessment of the risk (SR or NSR) and the rationale used in making the risk determination.
  - b) The IRB makes its own determination of the risk category (SR or NSR). The IRB reviews reports of prior investigations conducted with the device, the proposed investigational plan, a description of subject selection criteria, monitoring procedures, and any other information the IRB deems necessary to make its decision.
  - c) After the IRB makes the risk determination, the IRB conducts the review of the study using the same criteria it would use in considering approval of any full review application. The IRB considers the risks and benefits of the medical device compared to the risks and benefits of alternate devices or procedures as listed in the application.
  - d) The IRB may request that the PI consult with the FDA for an opinion as appropriate and request a determination letter.
  - e) If the IRB determines that a protocol submitted for approval involves a SR device, which has been deemed NSR by the sponsor, the IRB notifies the investigator who notifies the sponsor. The sponsor notifies the FDA that the IRB has made an SR determination. The PI may conduct as an SR investigation following FDA approval of an IDE application.
  - f) If the FDA determines that a study involves the use of a SR device, the PI must obtain an IDE and IRB approval before the study begins and must conduct the study in accordance with IDE requirements.
  - g) If the study is determined to be NSR by both the FDA and IRB, there is no requirement for submission of an IDE application to the FDA.
  - h) The IRB may approve or disapprove the proposed research based on local context and its responsibilities to protect human subjects in research even when approval of the device has been granted by the FDA.
  - i) The decision of the IRB (both risk assessment and approval) in correspondence sent to the PI and documented in the meeting minutes.
  - j) Devices may have an unanticipated problem or adverse event to subjects or others. An investigator submits to the sponsor and to the IRB a report of any unanticipated problems or adverse event to subjects or others occurring during an investigation.(according to the AE policy)

I. **Humanitarian Use Device (HUD)**

A Description

A Humanitarian Use Device (HUD) is a medical device that is intended to benefit patients in the treatment and diagnosis of diseases or conditions that affect fewer than 4,000 individuals in the United States. A HUD is considered somewhere between research and ordinary clinical practice. These devices do not undergo the same stringent requirements that investigational devices do, yet they may be recognized as the “approved” standard, and in some cases, preferred medical device. To use a HUD, a Humanitarian Device Exemption (HDE), must be obtained from the Food and Drug Administration (FDA) Because of the expected small market, there is little hope to be able to obtain efficacy data required by ordinary pre-market approval (PMA). An approved HDE authorizes marketing of the HUD. However, an HUD may only be used in facilities that have an established local institutional review board (IRB). The use of a HUD does not constitute a research protocol. However, Federal regulations require the IRB to approve and monitor an activity that is clearly not research (21 CFR 814.124).

B **IRB Application / Review for HUD**

- 1 The physician/investigator is responsible for obtaining IRB approval before the HUD is administered to or implanted in a patient.
2. All initial HUD submissions must be reviewed by a fully-convened IRB. The following items must be included in the original submission:
  - a) Humanitarian Use Device Form
  - b) Humanitarian Device Exemption Letter from the FDA
  - c) Proposed Informed Consent Document using the HUD template
  - d) Copy of patient brochures or education materials
  - e) Any other documentation received from the sponsor
3. If approval is granted, then IRB shall determine what interval for approval is appropriate based on the degree of risk, however not to exceed 365 days, consistent with section entitled “Continuing Review”.
4. The PI must only use the device within the scope of its labeling
5. All devices must be kept secure and only used by physician’s approved by the IRB
6. The PI must report any adverse reactions or unexpected events to the IRB for prompt review.

C **Off-Label Use of a HUD in Emergency and Compassionate Use Circumstances**

When either situation arises, the physician-investigator should determine if the situation meets the requirements for emergency use of the device

**D      Emergency Use of HUD**

## Description / Guidance

It is recognized that there may be circumstances in which “off-label” use of a HUD may be necessary to save the life or protect the well-being of a patient. FDA expects the physician to determine whether these criteria have been met, to assess the potential for benefits from the unapproved use of the device, and to have substantial reason to believe that benefits will exist. The physician may not conclude that an "emergency" exists in advance of the time when treatment may be needed based solely on the expectation that IDE approval procedures may require more time than is available.

Physicians should be aware that FDA expects them to exercise reasonable foresight with respect to potential emergencies and to make appropriate arrangements under the IDE procedures far enough in advance to avoid creating a situation in which such arrangements are impracticable

**E      Emergency Use Qualifications****1.** A patient should meet the following criteria:

- a) the patient is in a life-threatening condition that needs immediate treatment;
- b) no generally acceptable alternative for treating the patient is available; and
- c) because of the immediate need to use the device, there is no time to use existing procedures to get FDA approval for the use.

**2.** It is expected the physician will follow as many subject protection procedures as possible prior to use of the device.

These include:

- a) obtaining an independent assessment by an uninvolved physician;
- b) obtaining informed consent from the patient or a legal representative;
- c) notifying institutional officials as specified by institutional policies;
- d) notifying the Institutional Review Board (IRB);
- e) and obtaining authorization from the IDE holder, if an approved IDE for the device exists.

**3.** After-use Procedures

After an unapproved device is used in an emergency, the physician should:

- a) report to the IRB within five days [21 CFR 56.104(c)] and otherwise comply with provisions of the IRB regulations [21 CFR part 56];
- b) evaluate the likelihood of a similar need for the device occurring again, and if future use is likely, immediately initiate efforts to obtain IRB approval and an approved IDE for the device's subsequent use;
- c) and if an IDE for the use does exist, notify the sponsor of the emergency use,
- d) Or if an IDE does not exist, notify FDA of the emergency use (CDRH Program Operation Staff 301-594-1190) and provide FDA with a written summary of the conditions constituting the emergency, subject protection measures, and results.

4. Subsequent emergency use of the device may not occur unless the physician or another person obtains approval of an IDE for the device and its use. If an IDE application for subsequent use has been filed with FDA and FDA disapproves the IDE application, the device may not be used even if the circumstances constituting an emergency exist. Developers of devices that could be used in emergencies should anticipate the likelihood of emergency use and should obtain an approved IDE for such uses.

F **Compassionate use of a Humanitarian Use Device (subject to full board review.)**

1. Description:

FMC IRB may, at its discretion, approve a PI’s application for the compassionate use of a Humanitarian Use Device (HUD) when the following criteria are met.

2. Procedure:

Compassionate use shall be reviewed by the full IRB in a convened meeting using all standard full review criteria. In addition, the PI shall provide the HDE holder and the Forsyth Medical Center IRB with information addressing the criteria listed above. The approval applies to the single case requested and does not apply to a class of patients

3. Before the **device** is used, the physician will submit to FMC **IRB** the following:

- a) A copy of the compassionate use request sent to the HDE holder including:
- b) A description of the patient’s condition and circumstances necessitating treatment under compassionate use
- c) A discussion of why there are no alternative therapies available and why the probable risk of the investigational **device** is no greater than the probable risk from the disease or condition
- d) Identification of any deviations anticipated in order to treat the patient
- e) In addition, the PI shall request that the HDE holder submit an HDE amendment for FDA approval prior to the use of the device. If the FDA grants approval, the PI shall report the use of the HUD to the IRB and the HDE holder for subsequent submission to the FDA database
- f) Obtain letter from the HDE holder approving the compassionate use
- g) Copy of any FDA correspondence or telephone logs concerning / approving the compassionate use.
- h) Copy of the independent assessment obtained from an uninvolved physician
- i) Copy of the informed consent to be used with this patient
- j) The monitoring schedules to be followed during follow-up including any tests, procedures, and exams to be performed.

4. After Use

- b) Submit a follow-up report on the patient’s condition and information regarding the patient protection measures to the HDE holder.

**J. Investigator Responsibilities**

1. The Principal Investigator shall be provided a copy of the Forsyth Medical Center's Investigator's Handbook that contains the required application forms, overview of the IRB process, outline of Investigator's responsibilities and other pertinent information to facilitate the proposal application process.
2. Included in the application process, a Principal Investigator must complete the applicable forms as found in the IRB Handbook and submit a signed 'Statement of Investigator' in addition to a FDA form 1572 when applicable. Any revisions to the study after initial approval shall be re-submitted with any change in research activity or location. The Statement of Investigator or FDA form 1572 acknowledges his/her responsibilities as The Principal Investigator.
3. It is the Principal Investigator's responsibility to complete and process all documents required for the application, continuing review, serious/unexpected adverse event reports, and study termination within the time limits set forth by the committee when the proposal is approved.
4. Investigators, by accepting the approval of a project by this IRB, agree to:
  - a) Notify the IRB immediately of any death or other serious and/or life-threatening or unexpected adverse events or other problems that may place subjects or others at increased risk;
  - b) Inform the IRB promptly of any changes in the study that may be material to the IRB's duties and responsibilities. Changes in previously approved research may not be initiated without IRB review and approval.
  - c) It is the Investigator's responsibility to declare any material conflict of interests in relation to ownership or interests in the research protocol. A statement will be required in the Informed Consent Document that informs the subject of the Principal Investigator's material interest in the research.
5. It is the Investigator's responsibility to assure that although an investigator (or designee) may discuss availability of studies and the possibility of entry into a study with a prospective subject without first obtaining consent, informed consent must be obtained prior to initiation of any screening procedures that are performed solely for the purpose of determining eligibility for research.
6. It is the Investigator's responsibility to ensure that informed consent of the patient and/or appropriate surrogate consent is obtained per federal, state and institutional policies prior to commencing any study related procedure. The consent must be appropriately signed and dated by the patient and a witness. In addition, if a research assistant participated with the Principal Investigator or Sub-Investigator in the Informed Consent process, his/her signature is required. The exception to the required patient's signature would be if the patient is not able to participate in the consent process and the study has been approved for surrogate consent and/or waiver of consent under emergent conditions.
7. Documentation that adequate consent was obtained must be included in the patient's medical record.
8. Copy of the signed consent form is to be given to the patient or the surrogate that participated in representing the patient.
9. The Investigator will institute an advertising campaign, participant educational materials or media announcements using only materials that have been previously approved by the IRB.
10. If a Principal Investigator or Sub-Investigator has been suspended at another institution, or by another IRB, it is his/her responsibility to bring that action to the IRB's attention immediately.

**K. Expedited Review**

1. The IRB is required to review all requests for research. In some circumstances, the research will qualify for expedited review
2. “Categories of Research that may be reviewed by an Institutional Review Board (IRB) Through an Expedited Review” (November 9, 1998) OHRP guidance on the Use of Expedited Review Procedures (August 11, 2003) 63 FR 60364-60367:
  - a. Category 1:  
Research on drugs for which an investigational new drug application(21 CFR 312) is not required or research on medical devices for which a) an investigational device exemption application (21 CFR 812) is not required or b) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.
  - b. Category 2:  
Collection of blood samples by finger stick, heel stick, ear stick or venipuncture as follows: (a) from healthy, nonpregnant adults, who weigh at least 110 pounds. For these subjects, amounts drawn may not exceed 550 ml in an 8-week period and no more than 2 times per week; or (b) from other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml/kg in an 8-week period and collection may not occur more frequently than 2 times per week.
  - c. Category 3:  
Prospective collection of biological specimens for research purposes by noninvasive means. Examples: (a) hair and nail clippings in a nondisfiguring manner; (b) deciduous teeth at the time of exfoliation or if routine patient care indicates a need for extraction; (c) permanent teeth if routine patient care indicates a need for extraction; (d) excreta and external secretions (including sweat); (e) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue; (f) placenta removed at delivery; (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; (h) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques; (i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings; (j) sputum collected after saline mist nebulization.
  - d. Category 4:  
Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.) Examples: (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy; (b) weighing or testing sensory acuity; (c) magnetic resonance imaging; (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography; (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.
  - e. Category 5:

- Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis).
  - f. Category 6:  
Collection of data from voice, video, digital, or image recordings made for research purposes.
  - g. Category 7:  
Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.
  - h. Category 8:  
Continuing review of research previously approved by the convened IRB (a) where the research is permanently closed to the enrollment of new subjects, and all subjects have completed all research-related interventions, and the research remains active only for long-term follow-up of subjects; or (b) where no subjects have been enrolled and no additional risks have been identified; or (c) where the remaining research activities are limited to data analysis and report writing.
  - i. Category 9:  
Continuing review of research, not conducted under an investigational new drug application or an investigational device exemption where Category 2 through Category 7 do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.
- 2. The Chairperson may approve projects of minimal risk through the expedited review process as described in 45 CFR 46.110 and 21 CFR 56.110. Minimal risk is defined in federal regulations as "that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological tests."
- 3. The IRB delegates to the Chairperson the right to grant selected interim administrative approvals for minor changes in research projects previously approved by the full IRB during the period of approval provided these changes do not affect the risk to the patient.
- 4. All decisions made by the Chairperson by expedited review must be approved subsequently by the full IRB. These items will be reported and appear on the next meeting agenda.
- 5. Even if the regulations permit an activity to be handled by an expedited review, the Chairperson can deny the request whereby the item will receive full IRB review.
- 6. A proposal that qualifies for expedited review must be presented to the IRB using the standard application as if it required full IRB approval. This will be accompanied by an "Expedited Review Request" form (attachment "L") stating the reason that the Investigator feels the submitted materials qualify for expedited review.
- 7. The IRB chairperson shall review all applications to determine whether the submitted materials qualify for expedited review.
- 8. The IRB chairperson shall review the informed consent and application to confirm that it meets the guidelines for expedited review.
- 9. If the study qualifies for expedited review, the Chairperson may issue a letter of approval.
- 10. Research reviewed under the expedited review procedure is not necessarily eligible for waiver of informed consent. All research, regardless of whether it meets the

conditions for expedited review, must conform to the applicable requirements for obtaining and documenting informed consent.

11. The IRB chairperson may not disapprove an expedited request. If the chairperson is unable to provide approval, then the request will go to the full IRB for review.
12. The IRB office will process expedited materials in the same manner as materials requiring full IRB review.
13. The expedited approval will appear on the next meeting agenda and reported in the minutes.
14. Continuing review of an expedited study is required in the same manner as a study requiring full IRB review. The approval cannot be greater than a 12-month interval and may be more frequent as determined by the Chairperson at the time of approval.
15. The Investigator will follow all institutional and federal guidelines applicable with informed consent, documentation, and adverse event reporting applicable in studies requiring full IRB review.
16. If a study is initially approved via expedited approval then continuing review may also be processed by expedited review unless the Chairperson or the IRB determines that there is a change in the risk associated with the study such that it no longer qualifies for expedited review.
17. Advertisements should be reviewed and approved by the IRB as part of the package for initial review. However, when the clinical investigator decides at a later date to advertise for subjects, the advertising may be considered an amendment to the ongoing study. When such advertisements are easily compared to the approved consent document, the IRB chair, or other designated IRB member, may review and approve by expedited means, as provided by 21 CFR 56.110(b)(2). When the IRB reviewer has doubts or other complicating issues are involved, the advertising should be reviewed at a convened meeting of the IRB.

## **L. Exemption**

1. Certain types of human subjects' research may be exempted from review. However, because the involved investigators and NHTR facilities may be put at considerable risk if a study is inappropriately excluded from IRB review exemptions must be confirmed by the chair of the IRB or a designee upon review of applications for exemption. Since this constitutes a review, protocols that are deemed exempt are effectively "exempt from continuing review."
2. An investigator may not initiate research involving human subjects that the investigator believes is exempt until the investigator has received formal written concurrence of this exempt determination from the IRB. Changes to exempted studies must be reviewed by the IRB just as amendments to studies receiving expedited or convened IRB review. In some instances, changes to an exempted study may render it no longer exempt.
3. The FMC IRB must determine that a project is exempt, not the principal investigator. Any study that the FMC IRB believes is not exempt must receive either expedited or convened review by the FMC IRB.
4. If information comes to the attention of the IRB suggesting that there are factors increasing the sensitivity and/or potential risk to human subjects in research that otherwise would appear to qualify for exemption under the criteria listed above, the IRB may, in its own sole judgment, deem the protocol to be subject to expedited or convened IRB review.
4. While human subjects research involving prisoners is never exempt from IRB review, research activities involving other human subjects may be exempted from IRB review if the only involvement of human subjects fits within one or more of the

following categories (45 CFR 46.101(b)):

5.

**Categories for exemption**

- a. Category 1:  
 Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods; or
- b. Category 2:  
 Research not involving children that is limited to the use of educational tests, survey procedures, interview procedures or observations of public behavior unless information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation. This exemption does not apply to research involving children except for research involving observations of public behavior when the investigator does not participate in the activities being observed, or interact directly with the children. All other exemptions apply to research involving children. [45 CFR 46 101(b)(2) as modified by Subpart D 45 CFR 46.401 (b)]
- c. Category 3:  
 Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under Category 2 of this section, if: (i) The human subjects are elected or appointed public officials or candidates for public office; or (ii) federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter
- d. Category 4:  
 Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.
- e. Category 5:  
 Research and demonstration projects conducted by or subject to approval of a federal agency and designed to study, evaluate or otherwise examine some aspect of (i) Public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs..
- f. Category 6:  
 Taste and food quality evaluation and consumer acceptance studies, (i) if wholesome foods without additives are consumed or (ii) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

**M. Continuing Review**

- 1. The IRB will conduct continuing review of previously approved research projects at intervals appropriate to the degree of risk or other factors, but not less frequently than once per year. The Principal Investigator will be informed of the review interval required in the initial approval letter.

2. The IRB has the right to require review on a more frequent basis at any time and will be required to do so if frequent serious adverse events are reported; if the study presents the possibility of high financial cost to the participant or the institution; or if the study presents the risk of permanent disability that would not be present except for participation in the study.
3. Any change in the interval of the review process requires the action of the full IRB and will appear on the agenda and noted in the minutes.
4. Requests for renewal shall be made to the Chairperson using the “ Study Progress Report’ and will provide information on experience of the study to date, new scientific information pertinent to the appropriateness of the study and/or that changes the risk to the participant, number of participants enrolled and expected duration of study. It is the responsibility of the Principal Investigator to provide the IRB sufficient information for thorough review and evaluation. A separate report is required for each protocol.
5. The ‘ Study Progress Report’ and request for renewal must be signed by the Principal Investigator for consideration by the IRB. It will be accompanied by a blinded copy of the completed consent form for the most recently consented participant to verify use of the most current approved consent form version.
6. Full IRB review is required for the renewal of all studies that were approved by the full IRB. With the following exceptions:  
Where
  - a) the research is permanently closed to the enrollment of new subjects
  - b) all subjects have completed all research-related interventions and
  - c) the research remains active only for long-term follow-up of subjects; or
  - d) Where no subjects have been enrolled and no additional risks have been identified; or
  - e) Where the remaining research activities are limited to data analysis.
7. A study that was initially approved via expedited review is eligible for renewal by the expedited approval process
8. The actions the IRB may take upon review of the Continuing Review Report are to 'Approve', 'Close to Accrual', or ' Close.'  
The IRB may choose to Approve the study whereby the study would be eligible to remain active and open for enrollment; or not approve the study whereby the study would be 'Closed to Accrual' or ' Closed' and not eligible for enrollment.  
A 'Closed to Accrual study is closed to enrollment but is following the patients enrolled;  
A ' Closed' study means that all study activities have either been stopped or are completed and no patients remain enrolled.
9. Upon decision by the IRB the Principal Investigator will receive notification of the review process informing him/her of its decision regarding review of the study and a copy of the Informed Consent with a current valid date stamp.
10. If, after review of the Study Progress Report, the IRB determines that additional information is needed, or that irregularities have arisen which could affect the participation of the human subjects, the IRB may take one or more of the following actions:
  - a) Request revisions and/or additional information;
  - b) Request the Investigator to present findings at an IRB meeting;
  - c) Request consultation from individuals with expertise in specific area;
  - d) Review records and/or observe or authorize a third party to observe the research process, records and/or consent process;
  - e) Suspend approval pending further investigation by the IRB;
  - f) Terminate IRB approval;
  - g) Initiate audit of study.

11. A study that is not renewed prior to the expiration date will be placed on hold or closed by the IRB. The decision whether to place on hold or close the study is dependent on the status of the patients enrolled, the risk to the patients by continued participation and the status of the study from the sponsor or Principal Investigator.
12. **Reminder Notifications:**  
As a courtesy, when a research project is due for continuing review, a written reminder is sent from the IRB to the PI approximately 60 days before the date of continuing review. Another reminder may be sent approximately 30 days prior to the review date. If an application for renewal is not received from the PI by the expiration date, then the IRB will send an expiration notice to the PI. Copies of all reminders and expiration notices are kept in the study file
13. The Principal Investigator will be notified immediately in writing of the change in status of the study and be advised that no new subjects may be enrolled and a ' Study Progress Report is due within seven days from date of notice.
14. In addition, the funding agency and/or sponsor will be notified of the change in status of the study.
15. If a study is not renewed prior to the expiration date notification will be sent to the PI ordering that all study-related measures must immediately cease except those necessary for welfare of the human subjects; If the PI desires to continue a study that has lapsed for more than one month, then the PI must submit a new application for re-review by the IRB, and must wait for IRB approval before resuming research under the protocol.

**N. Revisions**

1. Revisions to an approved protocol that include more than minor changes, i.e. change in risk/benefit ratio, study procedures and/or costs require a review by the IRB and cannot be expedited. Administrative changes such as change in Investigators contact information may be handled in an expedited manner provided the administrative changes do not impact the risk to the participant. In this case, the request for review must be accompanied by the "Request for Expedited Review" form (attachment "L").
2. Revisions that impact the informed consent document will require a revised informed consent submitted with the revision. When the revision is approved the revised Informed Consent Document will become the valid consent and will be stamped and dated by the IRB Manager. Previously approved Informed Consent Documents will become invalid and the approved document will be sent to the Principal Investigator together with notification of review and approval.
3. The Principal Investigator may not implement a revision and/or amendment until it has been reviewed and a decision has been reached by the IRB unless there is immediate risk of harm to the subject 21 CFR 56.104(c)
4. The Principal Investigator must submit revisions and/or amendments in a timely manner. It is the Principal Investigator's responsibility to notify the IRB immediately if the revision and/or amendment involve risk to patients, whereby the Investigator may suspend continuing the study until the IRB can review the proposed amendment.

**O. Adverse Event Reporting**

1. It is the investigator's responsibility to report in writing within 24 hours of discovery to the IRB Chairperson and the FDA if applicable, any injuries to subjects, deaths associated with the research, or any unanticipated problems, which involve risks to the human research subjects or others.

2. An Adverse Event (also, Adverse Drug Experience [ADE] or Adverse Drug Reaction [ADR]) is defined as: Any deterioration in the health status of a subject or patient associated with the use of a drug in humans, whether or not considered drug related, including the following: any event occurring in the course of the use of a drug product in professional practice; any event associated with a drug overdose, whether accidental or intentional; any event associated with drug abuse; any event occurring from drug withdrawal; and any significant failure of expected pharmacological action.
  
3. Definitions Applicable to Investigational Drugs
  - a) Serious Adverse Event  
Any experience that suggests a significant hazard, contraindication, side effect or precaution, i.e., any experience that is fatal or life-threatening, is permanently or severely disabling, requires or prolongs inpatient hospitalization or is a congenital anomaly, or any important medical event that requires intervention to prevent any of the preceding definitions.
  - b) Unexpected Adverse Event  
Any adverse event that is not identified in nature, severity or frequency in the current investigator's brochure, or that is not identified in nature, frequency or severity in the risk information described in the general investigational plan.
  
4. Definitions Applicable to Marketed Drugs (FDA – approved)
  - a) Serious Adverse Event [See (a) above]
  - b) Expected Event  
An adverse event listed in the current approved labeling for the drug as having been reported or associated with the use of the drug.
  - c) Unexpected Event  
An adverse event not listed in the current labeling for the drug, including events that may be symptomatically or pathophysiologically related to an event listed in the labeling but differing from that listed event because of greater severity or specificity
  
5. Definitions Applicable to Investigational Devices
  - a) **Unanticipated Adverse Device Effect (UADE):**  
Unanticipated adverse device effect is any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects
  
6. All serious and unexpected adverse experiences will be reported to the IRB as part of the ongoing review process until the study is terminated or completed.

**P. Reporting Serious Adverse Events**

1. The IRB must be notified by any participating investigator of any and all Serious Adverse Events (SAE's) that are deemed promptly reportable according to 21 CFR 312.32.
2. It is the Investigator's responsibility to report all SAEs that are determined to be causally related to the study drug or device, to the IRB and the sponsor within twenty-four (24) hours of learning of the event, and to complete the reporting process within 48 hours.

3. Immediately upon learning of the event [within 24 hours] the IRB should receive notification via fax, phone, or e-mail with known pertinent information that includes the study name, patient information, treatment protocol, drug or investigational device involved, any injury to subjects and other information that would facilitate the decision by the Chairperson as to whether action should be taken to suspend the study due to unexpected risks to human subjects
4. Within 48 hours of a serious adverse event a Serious Adverse Event Report' (attachment "E") must be completed, signed by the Principal Investigator, and submitted to the IRB office. The report must be complete and include information as detailed above [Item (c)] and other known information including a complete description of the nature of the adverse reaction, a discussion of the implications for continuation of the study, whether the SAE was study related, whether the risk is explained adequately in the informed consent document, and any recommended changes that should be initiated in the informed consent document based upon this experience.
5. It is the responsibility of the Principal Investigator to file the SAE report to the sponsor, and confirm this action on the 'Serious Adverse Event Report' filed with the IRB. The Investigator may submit a copy of any report submitted to the sponsor or FDA attached to the 'Serious Adverse Event Report' but it cannot be substituted for the required IRB form.
6. Notification may be made by a research staff member on behalf of an investigator but the complete SAE report containing all relevant information must be signed by the Principal Investigator or designee when unavailable.
7. An adverse event may be considered serious by the clinical investigator without meeting the FDA criteria for that definition. In such situations, the investigator should record the intensity of the event as "severe." The opposite may also occur: a volunteer may be admitted for elective surgery that the investigator does not consider serious, but since "inpatient hospitalization" is, by definition, a "serious" event, an SAE report would be required.
8. All local serious adverse events will be reported to the full IRB including supporting documents. All non-local serious adverse events (IND Safety Reports, MedWatch reports) will be reported to the IRB in a summary manner with the complete report and supporting documents reported to the Chairperson or designee.
9. The Chairperson of the IRB will have the right to suspend temporarily any research activities in the purview of the IRB if untoward or unexpected adverse events occur or if the rights of human subjects is questioned, or protocol compliance is an issue.
10. The IRB may also suspend or discontinue research which is not being conducted according to its requirements or which is associated with unexpected serious risk to its subjects.
11. The Principal Investigator and Sponsor will be notified of the suspension by the IRB. The IRB will initiate a review of the issues in question and report its finding to the Investigator and other appropriate parties including sponsors and regulatory agencies. If this occurs, the proposal must be reevaluated by the full IRB at its next meeting and a decision whether to continue the study is made.
12. The IRB may elicit expertise from the scientific community, the sponsor, the FDA, community members or other individuals to assist in determining whether a study should continue.

**Q. Protocol Violations and Deviations**

1 **Background:**

Protocol violations and deviations occur when there is a variance in a research study between the protocol that has been reviewed and approved by the IRB and the actual performance within the research study.

A protocol violation or deviation may rise to the level of research misconduct. If any member of the research team or any other knowledgeable individual obtains information concerning violations or deviations that may be deemed Research Misconduct, he or she is obligated to report this information to one of the following: The Careline in the Triad Region, the Assurance Institutional Official, Research Administration or the NH Director of Audit and Corporate Compliance. Research Misconduct is addressed in the following Novant Health Policy number NH-LD-AD-210.

2. **Protocol Deviations that must be Reported Promptly to the IRB**

Unanticipated Problems Involving Risks to Subjects or Others.

Any protocol deviation that constitutes an “unanticipated problem that involves risks to the subjects or others must be reported promptly to the IRB, as follows:

When such deviations occur in an emergency, such as when a departure from the protocol is required to protect the life or physical well – being of a participant, the sponsor and the reviewing IRB must be notified as soon as possible, but in no event later than 5 days after the emergency occurs. [21 CFR 812.150(a)(4).]

An Investigator should not implement any deviation from, or changes of, the protocol without agreement by the sponsor and prior review and documented approval opinion from the IRB of an amendment, except where necessary to eliminate an immediate hazard to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), change of telephone number(s)). Per ICH guidelines GCP 4.5.2.

3. **Major, Non-emergent Deviations Without Prior Approval.**

When a deviation is non-emergent, but is nonetheless major (i.e., is not “administrative” or “minor” as defined below), the IRB expects the PI to obtain prior approval by requesting approval from the IRB. The occurrence of a major, non-emergent deviation without prior IRB approval is considered non-compliance and must be reported to the IRB promptly. A PI’s failure to report promptly any major, non-emergent deviation for which the PI did not obtain prior approval is itself an incident of non-compliance.

4. **Protocol Deviations that may be Reported to the IRB on the Continuing Review Application**

Administrative and Minor Deviations: PIs should report protocol deviations that do not “affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects” to the IRB in summary form as part of the Continuing Review progress report or more frequently as required by the Sponsor. Examples of administrative and minor deviations could potentially include the following (provided that in no respect does such deviation affect the rights, safety or welfare of any subject):

- follow up visits that occurred substantially outside the schedule because participant’s schedule could not accommodate the protocol schedule;
- blood samples obtained at times close to but not precisely at the time points specified in the protocol; or
- eliminating a blood draw from the list of procedures approved by the IRB.

5. **Procedures for IRB notification and response in case of protocol deviations**

The IRB will determine if additional actions or follow-up are required. Further actions might include: Seeking additional information from the sponsor, Discussion of protocol compliance with the principal Investigator, Audit of investigator’s site by the IRB, Increasing the frequency of continuing review period for the study, Suspension or termination of the study.

A copy of all correspondence / reports will be kept in the IRB files for the study.

**R. Single Use Approvals**

1. 'Single use' approvals may be necessary when an investigator wishes to use a protocol which does not have the prior approval of the IRB or when an investigational drug is to be used on a one-time basis.
2. All requests for single use must be made to the IRB in writing and include a written letter from the investigator citing the treatment protocol, drug or investigational device that is to be used, the name of the patient and the circumstances that require that it be used prior to the next regular IRB meeting.
3. The written request should be accompanied by a sample consent form and complete application.
4. The IRB chairperson will review the written documentation to see that the informed consent meets the guidelines established by the committee. The Chairperson will also verify that the Principal Investigator has not made multiple, single-use requests for the same drug or procedure. If the request meets the consent form requirements, then the Chairperson will determine whether or not the requests qualifies for expedited review or single use approval review.
5. For all single use approvals a simple majority of the voting members of the IRB is required. This contact can be made by telephone, fax, e-mail or in writing, depending upon the urgency of the request. If the calls are made by telephone a record shall be made stating who was contacted and their vote. This record will become part of the IRB minutes. If a majority of the members vote yes, then the investigator will be notified by telephone and in writing that the approval has been obtained. A minimum of one physician must be involved in the approval process.
6. The Principal Investigator shall be notified in writing and by telephone if appropriate, of the single use approval. If appropriate, the protocol sponsor or the drug sponsor will receive a copy of that notification.

7. All documents for the study will be maintained in the usual manner in the IRB office.
8. Each single use approval shall be reported at the next IRB meeting by appearing on the agenda and reported in the subsequent minutes.
9. A single use protocol can be approved for a maximum of twelve (12) months. A more frequent renewal period may be determined by the Chairperson and/or recommended by the IRB.
10. The single use protocol requires an 'Continuing Review Report' to be completed with a request for renewal prior to the end of the approval period following the standard format for non-single use protocols.
11. An annual report of all single use approvals shall be presented to the IRB at the February meeting. It shall include all single use approvals for the previous calendar year.

**S. Informed Consent**

1. Informed Consent is considered to be a process whereby the Principal Investigator communicates to the human subject the details of the research study, the risk/ benefits of participation and his/her rights as a human subject. The Informed Consent should be viewed as an ongoing process between the Principal Investigator/research staff and the subject.
2. The Informed Consent document is the written format that is intended to reiterate the elements reviewed with the subject and to provide documentation of the process.
3. The Informed Consent document should not represent the process in its entirety but rather the written portion of the process.
4. Informed Consent is required from all research participants with the exception of studies that qualify under surrogate consent or waiver of consent under emergent conditions as provided by FDA guidelines.
5. Investigators may use the IRB's 'Informed Consent Document Template' as a model for each protocol's informed consent. Each section of the informed consent statement shall be completed as it pertains to the particular study.
6. The Informed Consent Document must be in the language understandable to the subject. When the prospective subject is fluent in English, and the consent interview is conducted in English, the consent document should be in English. However, when the study subject population includes non-English speaking people so that the investigator or the IRB anticipates that the consent interviews are likely to be conducted in a language other than English, the IRB should assure that a translated consent form is prepared and that the translation is accurate. A consultant may be utilized to assure that the translation is correct. If subjects of limited proficiency in their spoken language are enrolled, the Investigator must assure an appropriate mechanism is in place to allow adequate consent.
7. The informed consent shall include the following basic elements:
  - a) Statement that the study involves research
  - b) Explanation of the purpose of the research
  - c) Expected duration of subject's participation
  - d) Description of the procedures to be followed and identification of any procedures which are experimental
  - e) Description of the possible risks and discomforts to the subject including financial risks
  - f) Description of the benefits to the subject or to others including financial benefits, amount and method of payment
  - g) Disclosure of alternative procedures, treatments or therapies, if any, that may be advantageous in lieu of that offered in the study;

- h) A valid authorization for the release of protected health information that includes:
    - a) A description of the information to be gathered
    - b) Who may use or disclose the information
    - c) Who may receive the information
    - d) The purpose of the use or disclosure
    - e) Expiration date or event
    - f) Individual's signature and date
    - g) Right to revoke authorization
    - h) Right to refuse to sign authorization
    - i) Re-disclosures not protected
    - j) Provide statement that patient cannot be required to sign the authorization in order to receive treatment, payment or enroll or be eligible for benefits
    - k) Signature of the patient or patient's representative (clearly define relationship) and date
  - i) Statement that the FDA and the IRB may inspect the records
  - j) Explanation of whom to contact if questions arise or if injury occurs
  - k) Statement that participation is voluntary, that refusal to participate involves no penalty or loss of benefits, and that subject may withdraw at any time without penalty or loss of any benefits
  - l) Statement that the procedure may involve unforeseeable risks
  - m) Statement that the subject's participation may be terminated by the investigator without subject's consent
  - n) Statement or explanation of whether any compensation and/or medical treatment is available in the event of injury, and , if so, what is available or where further information can be obtained, and who is financially responsible
  - o) Additional costs to subject resulting from participation in research, including, if any, medical bills not covered by insurance, time involved in participation, transportation, and all related expenses
  - p) Statement of Investigator's financial interest when applicable
  - q) Consequences, if any, of patient's decision to withdraw from research
  - r) Statement that significant new findings developed during research, which may relate to subjects' willingness to continue, will be provided to subject
  - s) Approximate number of subjects involved in study
  - t) Statement that study participation may involve risk to an embryo or fetus if capable of becoming pregnant
  - u) Consequences of withdrawal by the subject (if any), and procedures for orderly termination of the subject's participation
  - v) In the footer section of each page of the consent, include the month and year the document is created; if the consent is revised, the revision date must appear
  - w) Page numbering should include the format "page x of y" in the footer section of each page of the consent form
  - x) The footer section of each page should also include a provision for the subject to initial each page
  - y) Statement that participant has had opportunity to ask questions and all questions have been answered to their satisfaction
  - z) Statement that participant has read the consent form or had it read to them with an impartial witness present
8. The Informed Consent must be signed and dated by the subject or his/her representative. The witness must also sign the consent form. The witness' signature is to confirm that the patient signed the form, and does not imply any verification that the patient was appropriately consented, nor that the patient understands the content of the consent.

9. The patient should initial each page where indicated as evidence that they have read and reviewed the material.
10. If research staff other than the Principal Investigator assisted in the consent process, their signature should be included on the consent.
11. If the patient can speak and understand English, but cannot read the consent form, then it should be read to the patient with an impartial witness and the patient 'make their mark' whether that be signature or "X" if unable to sign their name.
12. A copy of the form must be given to the person signing the form.
13. A copy of the translated consent document must be given to each appropriate subject. While a translator may be used to facilitate conversation with the subject, routine ad hoc translation of the English consent document may not be substituted for a written translation.
14. An Informed Consent document requires a stamp from the IRB indicating the date of approval to be considered valid.
15. Only valid consent forms are to be used to in the consent process.
16. The consent forms should be written in such a manner as to assist the patient in being able to understand the information. It should appear in language targeted at the 8<sup>th</sup> grade reading level, should include explanation of scientific terms and procedures and be sufficient in length to cover the required elements, but not to the extent that it creates confusion for the patient.

**T. Surrogate Consent**

1. Surrogate Consent is permissible under certain circumstances whereby the patient is unable to participate in the consent process and a surrogate represents him/her.
2. The IRB will permit Surrogate Consent provided certain conditions are satisfied
3. The use of Surrogate Consent as an option for a protocol requires that the Principal Investigator indicate the request at the time of application, and provides documentation to support the validity of his/her request.
4. The IRB requires the following when implementing an approved Surrogate Consent:
  - a) Principal Investigator (PI) or sub-investigator will document in medical record his/her determination that the patient is not able to participate in the informed consent process and include a statement explaining the reason.
  - b) A physician on staff at the facility not involved with the research study will be required to confirm that the patient is cognitively impaired and not able to participate in the informed consent process. The consulting physician will document his/her validation in the medical record.  
For patients who are determined to be unable to participate in the consent process, written consent may be obtained from a surrogate. A surrogate will be identified based on the following priority in descending order:
    - (1) Healthcare agent acting under a healthcare power of attorney
    - (2) Spouse or legal guardian
    - (3) The unanimous consent of all adult children from whom written consent may be obtained by the Principal Investigator within a time period specified in the application to the IRB.
    - (4) Any parent or step-parent;
    - (5) Any adult sibling
  - d) Clinical staff will document in the patient's record attempts to contact each potential surrogate in the descending order listed above. If consent is not obtained from any of the designated surrogates, the patient will not be eligible for the study. If a family member refuses to give surrogate consent, no other attempt should be made to obtain consent. Faxed signatures are acceptable. Verbal consents are not sufficient

5. For a patient with a living will, it should be determined whether participation will be consistent with the patient’s intentions. If participation would be inconsistent with the patient’s intentions as set forth in the living will, the patient cannot participate.
6. The Principal Investigator or the participating Sub-Investigator will be responsible for notifying the IRB within 72 hours that he has implemented Surrogate Consent. He will provide the name of the protocol, name of patient and date of consent.
7. The Principal Investigator or the participating sub-investigator will assess patient’s mental status and at the earliest time that the patient is deemed not to be cognitively impaired, he will consider the Surrogate Consent no longer valid and present the informed consent to the patient for their voluntary participation. The patient may refuse any further participation at this time.
8. The PI or the participating sub-investigator will notify IRB within 72 hours when a patient is no longer participating under Surrogate Consent.
9. Surrogate Consent cannot be substituted for Waiver of Consent Under Emergent Conditions

**U. Waiver of Consent Under Emergent Conditions**

1. Under certain emergent conditions a waiver of consent can be authorized. These include:
  - a) The patient is in need of emergency medical intervention, but cannot give consent because of this condition. The condition is life threatening and the situation is emergent.
  - b) The patient does not have a legally authorized person to represent them.
  - c) Available treatments are unproved or unsatisfactory. *“When the relative benefits and risks of the proposed intervention, as compared to standard therapy, are unknown, or thought to be equivalent or better, there is clinical equipoise between the historic intervention and the proposed test (research intervention)”*(60 FR 49086 at 49093, September 21, 1995)
  - d) There is no reasonable method to determine which individual is likely to participate.
2. When these conditions are satisfied the Principal Investigator may submit a protocol requesting waiver of the informed consent process.
3. In addition to the normal application process, the following conditions will be required for review:
  - a) A physician member of the IRB who is not participating in the clinical investigation must participate in the IRB deliberation and vote affirmatively for the study.
  - b) There must be collection of valid scientific data to determine the safety and effectiveness of the research intervention.
  - c) The IRB must determine what procedures the investigator should follow to determine that informed consent cannot be obtained.
  - d) Appropriate animal and other pre-clinical studies have been conducted
  - e) Risks are reasonable in relation to what is known about the condition being studied, and the proposed intervention or activity.
  - f) The study could not be practically performed without waiver of informed consent.
4. The facility proposing to be engaged in the research study must verify that the proposed research study has been registered with the North Carolina Medical Care Commission.
5. Prior to the start of the community consultation process, the facility must give notice to the North Carolina Medical Care Commission. The notice must include the following information

- a. The title of the research study;
  - b. A description of the research study, including a description of the population to be enrolled;
  - c. A description of the planned community consultation process, including currently proposed meeting dates and times;
  - d. An explanation of the way that people choosing not to participate in the research study may opt out; and
  - e. Contact information including mailing address and phone number for the IRB and the principle investigator
6. The North Carolina Medical Care Commission may publish all or part of the above information in the NC Register and may require the facility proposing to conduct the research study to attend a public meeting of the Commission to present and discuss the study or the community consultation process proposed.
7. The Principal Investigator must hold a public forum, seminar or conference prior to the IRB meeting where the protocol will be reviewed. The public forum must be advertised at least three times in the appropriate newspaper or newsletter targeting the subjects. At least one advertisement must be on the weekend. The forum must include the information listed below. It may also include educational information about the research process in general, the role of the IRB, the regulations guiding clinical research and the medical condition being addressed. The researcher may not pay the participants or offer an inducement to promote attendance to the forum.
8. The community consultation should include:
- a) Consultation must occur prior to IRB review of the protocol
  - b) Consultation must include community representatives with the same demographic characteristics as the target subjects.
  - c) Content of information to be disclosed during public consultation must include:
    - (1) why condition is life threatening and emergent;
    - (2) the scientific need to conduct the study;
    - (3) the research procedures that will be used;
    - (4) the other locations where the study is currently being done;
    - (5) the sponsor of the study
    - (6) a description of the target subjects
    - (7) methods used to identify subjects
    - (8) information included in the proposed written informed consent;
    - (9) how study will be advertised;
    - (10) how the researcher will explain the study to the patient when the patient is able to participate or to a legally authorized representative should the patient remain incapacitated
    - (11) Identify who will serve as external data monitor
9. The application must include documentation of community consultation in coordination with the IRB. There must be a written summary of the community consultation. A videotape may be used, but it does not replace the written summary.
10. This summary is presented to the IRB as part of application for full committee review.
11. There must be an IRB approved informed consent with recognition on the application that Emergency Consent may be required.
12. The IRB will use Forsyth Medical Center's hierarchy of legal representatives, unless it specifies otherwise.

13. The investigator must attempt to contact a legally authorized representative for each subject within an IRB specified time (if the IRB determines it is appropriate to attempt to obtain surrogate consent within a potential therapeutic window of time) and document those attempts in the medical record, the research study records and on IRB continuing review forms.
14. The investigator will assure that the sponsor provide the IRB with a separate IDE or IND number.
15. The sponsor must disclose to the IRB the decisions of other IRBs not to permit emergency informed consent.
16. The sponsor or Principal Investigator must submit to the IRB a procedure to inform the patient of his/her participation when the patient is able to comprehend.
17. If the patient remains incapacitated, then the sponsor or PI is responsible for ensuring that a legal representative of the patient or if a legal representative is not available, a family member, is informed of the patient's inclusion in the clinical investigation, the details of the investigation and other information contained in the informed consent document.
18. If the patient dies before a legally authorized representative or family member can be contacted, information of the patient's inclusion in the clinical investigation, the details of the clinical investigation, and other information contained in the informed consent document will be provided to the patient's legally authorized representative or family member, if feasible and documented in the medical record.
19. If any legally authorized representative or family member objects to a patient's participation in the clinical investigation, the patient will not participate.
20. The sponsor or clinical investigator must submit a process to the IRB for disclosing the results of the study to the community upon completion of the study. The summary will include the age, gender and race of the research population (*21 CFR 50.24, 7 iii*)

**V. Records and Reports**

1. The IRB Manager will be responsible for maintaining all records for IRB operations.
2. The records maintained for each proposal will include, but are not limited to:
  - a) Copies of the operating procedure (protocol);
  - b) The original research proposal for all proposals reviewed, including sample consent documents;
  - c) The "Request for IRB Services" Proposal (attachment "A").
  - d) Amendments and revisions to protocol;
  - e) Investigator's Statement and/or Form 1572;
  - f) Investigator's Brochure [if applicable];
  - g) Reports of continuing review;
  - h) Deliberations and decisions of the full committee;
  - i) The 'Continuing Review Reports'
  - j) Relevant correspondence concerning each proposal;
  - k) Scientific evaluations submitted with each proposal;
  - l) Serious Adverse Event reports;
  - m) Communications from participants to the IRB office regarding the study;
  - n) Copy of original and revised/updated Informed Consent documents with valid IRB date stamp;
  - o) Organizational Impact/Costs Statement
  - p) Statements of significant new findings that are provided to participants during study process;
  - q) Educational and/or informational materials provided to participants that have been approved by the IRB;
  - r) Copies of advertisements that have been approved by the IRB;

- s) Records of demonstration of community participation if required by protocol;
  - t) Emergency use reports;
  - u) Final report at closure of study;
  - v) Audit report [if applicable];
3. IRB operation files will be maintained separate from protocol files. Administrative files will include but are not limited to:
- a) Copies of IRB's Policy and Procedure Manual, pertinent federal and regulatory references, meeting agendas, minutes and all communications with IRB Members;
  - b) Current IRB Roster;
  - c) Current Meeting Schedule;
  - d) Copies of all correspondence between the IRB, sponsors, regulatory agencies, research organizations, and investigators;
  - e) Copies of administrative policies and procedures pertinent to the internal operations of the IRB office [i.e. reporting, etc.];
  - f) Copies of all educational materials distributed to the IRB, and supporting reference documents as available;
4. The IRB minutes, IRB members present and absent from the meeting, discussions of protocols to include the recommended revisions, reasons for action or basis of deferring action, verbal approvals and/or voting, controversial issues regarding the research and/or consent process, educational and informational exchanges and the approval of minutes and other items. The minutes will also record the ballot votes for each pertinent agenda item.
5. The IRB Manager will prepare annual summary documents which are reviewed by the Chairperson and presented to the IRB and when applicable, submitted to the Medical Board. Annual reports include but are not limited to:
- a) Activity statistics indicating number of studies submitted, number approved, number closed, number terminated, number of revisions, adverse events and single use protocols.
  - b) Summary of critical issues addressed by the IRB during preceding year, changes in regulations, educational opportunities provided to IRB, revisions in policies and procedures, compliance audit activities and key items for upcoming year.
  - c) Summary of audits including number of studies and findings.
6. The Chairperson or the IRB may request any additional reports be submitted to administration, the Medical Staff and or researchers in the interest of improving operations, providing education, or informing appropriate parties of changes in policies or regulatory issues
7. All files will be made available for inspection by duly authorized representatives of federal, state or the institution. All records related to research proposals will be retained for a minimum of three (3) years after the research project is completed or canceled, or for the time period that is indicated by the sponsor, institution, or regulatory agency.
8. Files will be maintained in a secure, locked manner to preserve confidentiality. IRB files are to be separate documents that are maintained independent of any other research file. Access to the file is limited to authorized staff.

## **W. Vulnerable Populations**

1. Certain groups, such as racial minorities, the economically disadvantaged, the very ill, 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.
2. It is the responsibility of the IRB to initiate additional safeguards to protect the rights of vulnerable populations. Vulnerable populations include:
  - Prisoners;
  - Illiterate persons;
  - Minorities;
  - Economically disadvantaged;
  - Children (see Section X below for ADDITIONAL requirements);
  - Women
  - Patients with potentially terminal illness
3. The IRB will review studies that specifically target and/or potentially will include a vulnerable population under the following additional guidelines:
  - a) There is a representative on the IRB that can appropriately represent the population with background and experience to serve in such capacity including all other requirements of 45 CFR Subtitle A, Subpart C
  - b) If there is not appropriate representation on the IRB, then a person who meets the requirements will be ask to participate in the review process and will continue to consult with the IRB throughout the course of the study.
  - c) Informed Consent is reviewed with special attention given to the language, appropriateness for surrogate consent, need for a child's Informed Assent document and reading level of document.
  - d) Special provision may be required in the informed consent process when comprehension is severely limited, for example, by conditions of immaturity or mental disability. This may include surrogate consent and/or a provision that requires testing the comprehension of the consenting participant prior to initiating the study
  - e) Each class of subjects that one might consider as incompetent should be considered on its own terms.
4. Even for these persons, respect requires giving them the opportunity to choose to the extent that they are able, whether or not to participate in research. The objections of these subjects to involvement should be honored.
5. 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.

**X. Additional Safeguards for Children**

In addition to the requirements set forth above with respect to research involving vulnerable populations, research involving children must also meet the following criteria:

1. **Risk/Benefit analysis** – the IRB must make certain determinations when reviewing research involving children. IRB records must reflect the IRB’s understanding and justification for the risks and benefits posed by approved research involving children. Proposed research must fall within one of the four following categories:
  - a) Research not involving greater than minimal risk;
  - b) Research involving greater than minimal risk, but presenting the prospect of direct benefit to the individual subjects;
  - c) Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalized knowledge about the subject’s disorder or condition; or
  - d) Research not otherwise approvable, which presents an opportunity to understand, prevent or alleviate a serious problem affecting the health or welfare of children.

Each of these four categories stipulates specific conditions for approval. The IRB must determine and document the Pediatric Risk Level for each proposal involving children. Categories of Research and Pediatric Risk Levels are summarized in Table 1 below.

**2. Parental Permission and Assent by the Child** – In addition to obtaining consent from the parent, the IRB must determine that adequate provisions are made for soliciting the assent of the children who are being considered for participation in research.

a. **Capability of assent** - In determining whether children are capable of providing assent, the IRB shall take into account the ages, maturity and psychological state of the children involved. This judgment may be made for all children to be involved in research under a particular protocol, or for each child, as the IRB deems appropriate. If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research, the assent of the children is not a necessary condition for proceeding with the research.

b. **Waiver of Assent requirement** - Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement where (a) the research involves no more than minimal risk; (b) the waiver will not adversely affect subjects’ rights and welfare; (c) the research could not practicably be carried out without the waiver; and (d) when appropriate, the subjects will be provided with pertinent information after participation. When the IRB waives the requirement for the child’s assent in a study, the parents’ permission is still required.

**3. Wards** – Children who are wards of the state or other agency/institution/entity may be included in research only if the following criteria are met:

a. **Type of research** – the research must either be related to their status as wards or be conducted in schools, camps, hospitals, institutions or similar settings in which the majority of children involved as subjects are not wards.

b. **Appointment of advocate** – the IRB must require appointment of an advocate for each child who is a ward.

- 1) The advocate will serve in addition to any other individual acting on behalf of the child as guardian or person standing in loco parentis.
- 2) One individual may serve as advocate for more than one child.
- 3) The advocate must be an individual who has the background and experience to act in, and agrees to act in, the best interest of the child for the duration of the child’s participation in the clinical investigation.
- 4) The advocate must not be associated in any way (except in the role as advocate or member of the IRB) with the clinical investigation, the investigator(s), or the guardian organization.

**Y. Compliance**

1. Compliance with Forsyth Medical Center IRB, federal, state and institutional policies are expected at all times by Principal Investigators. The IRB office will perform quality review processes and/or compliance audits aimed at identifying areas of improvement. Identifying non-compliance and creating an environment that promotes research being conducted in an ethical and scientific manner is the purpose of compliance audits.
2. It is the Principal Investigator's responsibility to report any research misconduct or non-compliance to the IRB immediately upon learning of the event(s). This includes complying with all applicable federal, state, ICH and institutional regulations and guidelines; adherence to approved protocol; reporting of revisions to protocol before initiating; submitting documents to IRB in timely manner; misuse or non-use of informed consent; prompt notification of serious/unexpected adverse events; and other activities which demonstrate unethical practice or unsound judgment in the execution of the research project and/or whereby patients safety and human rights are violated.
3. The IRB is responsible for providing oversight on the conduct of approved research protocols. The IRB has the right to observe the Principal Investigator, Sub-Investigator and other research staff in the process of conducting the research study including the informed consent process, research procedures, and documentation. The IRB may choose to monitor the activities by appointing members of the IRB, or may elect to have a representative with expertise in the area provide the oversight.
4. Upon notification to the IRB of possible misconduct or non-compliance or, at the time the IRB becomes aware of a potential issue in misconduct or non-compliance. The Novant Corporate Policy on Research Misconduct (NH-LD-AD-210) will be implemented.

5. Research Misconduct is defined as:  
Fabrication, falsification or plagiarism in proposing, performing, or reviewing research, or in reporting research results.
  - II. Fabrication is making up data or results and recording or reporting them.
  - III. Falsification is manipulating research materials, equipment, or processes, or changing or omitting data or results such that the research is not accurately represented in the research record.
  - IV. Plagiarism is the appropriation of another person's ideas, processes, results, or words without giving appropriate credit.
  - V. Research misconduct does not include honest error or differences of opinion.42 CFR Part 93, Sec. 93.103
6. The IRB will report any non-compliance with its requirements as may be required by 45 CFR 46.108(c) or other authorities. This includes reporting to the Medical Board, Department Chair, the sponsor, FDA and OHRP.
7. The IRB will report its decision in writing to the Principal Investigator. The Principal Investigator may request an opportunity to address the IRB or the IRB may request the Principal Investigator to be available to the IRB for discussion.
8. IRB actions cannot be overridden by individuals, another IRB, groups or administration.
9. Following a suspension of an Investigator, he/she must apply to the IRB for approval and reinstatement.
10. Any disciplinary action by federal or state regulatory agencies or by the Medical Board that prohibit a physician from participating in research activities will be recognized by the IRB and the investigator will be considered ineligible. No action by the IRB can supersede the action by a regulatory agency that defines the scope of responsibility of the IRB.

## V. DOCUMENTATION

Documentation of the approval process will be maintained in the IRB meeting minutes

## VI. DEFINITIONS

**ADJUVANT THERAPY** Therapy provided to enhance the effect of an primary therapy; auxiliary therapy.

**ADVERSE EFFECT** An undesirable and unintended, although not necessarily unexpected, result of therapy or other intervention (*e.g.*, headache following spinal tap or intestinal bleeding associated with aspirin therapy).

**ASSENT** Agreement by an individual not competent to give legally valid informed consent (*e.g.*, a child or cognitively impaired person) to participate in research.

**ASSURANCE** A formal written, binding commitment that is submitted to a federal agency in which an institution promises to comply with applicable regulations governing research with human subjects and stipulates the procedures through which compliance will be achieved [Federal Policy [[section]]\_\_\_\_.103].

**AUTHORIZED INSTITUTIONAL OFFICIAL** An officer of an institution with the authority to speak for and legally commit the institution to adherence to the requirements of the federal regulations regarding the involvement of human subjects in biomedical and behavioral research.

**AUTONOMY** Personal capacity to consider alternatives, make choices, and act without undue influence or interference of others.

**AUTOPSY** Examination by dissection of the body of an individual to determine cause of death and other medically relevant facts.

**BELMONT REPORT** A statement of basic ethical principles governing research involving human subjects issued by the National Commission for the Protection of Human Subjects in 1978.

**BENEFICENCE** An ethical principle discussed in the *Belmont Report* that entails an obligation to protect

persons from harm. The principle of beneficence can be expressed in two general rules: (1) do not harm; and (2) protect from harm by maximizing possible benefits and minimizing possible risks of harm.

**BENEFIT** A valued or desired outcome; an advantage.

**BIOLOGIC** Any therapeutic serum, toxin, anti-toxin, or analogous microbial product applicable to the prevention, treatment, or cure of diseases or injuries.

**BLIND STUDY DESIGNS** *See: Masked Study Designs; Double-Masked Design; and Single-Masked Design.*

**CASE-CONTROL STUDY** A study comparing persons with a given condition or disease (the cases) and persons without the condition or disease (the controls) with respect to antecedent factors. (*See also: Retrospective Studies.*)

**CHILDREN** Persons who have not attained the legal age for consent to treatment or procedures involved in the research, as determined under the applicable law of the jurisdiction in which the research will be conducted [45 CFR 46.401(a)]. In North Carolina, a child is an individual under the age of 18 unless he or she has been emancipated. A child becomes emancipated when he or she marries, serves in the United States Armed Forces or obtains a judicial decree declaring emancipation.

**CDC** Centers for Disease Control and Prevention; an agency within the Public Health Service, Department of Health and Human Services.

**CLASS I, II, III DEVICES** Classification by the Food and Drug Administration of medical devices according to potential risks or hazards.

**CLINICAL TRIAL** A controlled study involving human subjects, designed to evaluate prospectively the safety and effectiveness of new drugs or devices or of behavioral interventions.

**COGNITIVELY IMPAIRED** Having either a psychiatric disorder (*e.g.*, psychosis, neurosis, personality or behavior disorders, or dementia) or a developmental disorder (*e.g.*, mental retardation) that affects cognitive or emotional functions to the extent that capacity for judgment and reasoning is significantly diminished. Others, including persons under the influence of or dependent on drugs or alcohol, those suffering from degenerative diseases affecting the brain, terminally ill patients, and persons with severely disabling physical handicaps, may also be compromised in their ability to make decisions in their best interests.

**COHORT** A group of subjects initially identified as having one or more characteristics in common who are followed over time. In social science research, this term may refer to any group of persons who are born at about the same time and share common historical or cultural experiences.

**COMPENSATION** Payment or medical care provided to subjects injured in research; does not refer to payment (remuneration) for participation in research. (*Compare: Remuneration.*)

**COMPETENCE** Technically, a legal term, used to denote capacity to act on one's own behalf; the ability to understand information presented, to appreciate the consequences of acting (or not acting) on that information, and to make a choice. (*See also: Incompetence, Incapacity.*)

**CONFIDENTIALITY** Pertains to the treatment of information that an individual has disclosed in a relationship of trust and with the expectation that it will not be divulged to others without permission in ways that are inconsistent with the understanding of the original disclosure.

**CONSENT** *See: Informed Consent.*

**CONTRACT** An agreement; as used here, an agreement that a specific research activity will be performed at the request, and under the direction, of the agency providing the funds. Research performed under contract is more closely controlled by the agency than research performed under a grant. (*Compare: Grant.*)

**CONTROL (SUBJECTS) or CONTROLS** Subject(s) used for comparison who are not given a treatment under study or who do not have a given condition, background, or risk factor that is the object of study. Control conditions may be concurrent (occurring more or less simultaneously with the condition under study) or historical (preceding the condition under study). When the present condition of subjects is compared with their own condition on a prior regimen or treatment, the study is considered historically controlled.

**CONTRAINDICATED** Disadvantageous, perhaps dangerous; a treatment that should not be used in certain individuals or conditions due to risks (*e.g.*, a drug may be contraindicated for pregnant women and persons with high blood pressure).

**CROSS-OVER DESIGN** A type of clinical trial in which each subject experiences, at different times, both the experimental and control therapy. For example, half of the subjects might be randomly assigned

first to the control group and then to the experimental intervention, while the other half would have the sequence reversed.

**DATA AND SAFETY MONITORING BOARD** A committee of scientists, physicians, statisticians, and others that collects and analyzes data during the course of a clinical trial to monitor for adverse effects and other trends (such as an indication that one treatment is significantly better than another, particularly when one arm of the trial involves a placebo control) that would warrant modification or termination of the trial or notification of subjects about new information that might affect their willingness to continue in the trial.

**DEAD FETUS** An expelled or delivered fetus that exhibits no heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, or pulsation of the umbilical cord (if still attached) [45 CFR 46.203(f)]. Generally, some organs, tissues, and cells (referred to collectively as fetal tissue) remain alive for varying periods of time after the total organism is dead.

**DEBRIEFING** Giving subjects previously undisclosed information about the research project following completion of their participation in research. (Note that this usage, which occurs within the behavioral sciences, departs from standard English, in which debriefing is obtaining rather than imparting information.)

**DECLARATION OF HELSINKI** A code of ethics for clinical research approved by the World Medical Association in 1964 and widely adopted by medical associations in various countries. It was revised in 1975 and 1989.

**DESCRIPTIVE STUDY** Any study that is not truly experimental (*e.g.*, quasi-experimental studies, correlational studies, record reviews, case histories, and observational studies).

**DEVICE (MEDICAL)** *See: Medical Device.*

**DHHS** A federal agency: U.S. Department of Health and Human Services; formerly the Department of Health, Education and Welfare (DHEW).

**DIAGNOSTIC (PROCEDURE)** Tests used to identify a disorder or disease in a living person.

**DOUBLE-MASKED DESIGN** A study design in which neither the investigators nor the subjects know the treatment group assignments of individual subjects. Sometimes referred to as "double-blind."

**DRUG** Any chemical compound that may be used on or administered to humans as an aid in the diagnosis, treatment, cure, mitigation, or prevention of disease or other abnormal conditions.

**EMANCIPATED MINOR** A minor who is free from the control of others. (Following statutory procedures, a judge issues an emancipation decree). A certified copy of the emancipation decree must become part of the medical record. Emancipated minors are those who have been married, are serving in the United States armed forces or have been emancipated by judicial decree. (N.C.G.S. 7B-3402; 7B-3509). (*See also: Mature Minor.*)

**EMBRYO** Early stages of a developing organism, broadly used to refer to stages immediately following fertilization of an egg through implantation and very early pregnancy (*i.e.*, from conception to the eighth week of pregnancy). (*See also: Fetus.*)

**EPIDEMIOLOGY** A scientific discipline that studies the factors determining the causes, frequency, and distribution of diseases in a community or given population.

**EQUITABLE** Fair or just; used in the context of selection of subjects to indicate that the benefits and burdens of research are fairly distributed [Federal Policy [[section]]\_\_\_.111(a)(3)].

**ETHICS ADVISORY BOARD** An interdisciplinary group that advises the Secretary, HHS, on general policy matters and on research proposals (or classes of proposals) that pose ethical problems.

**ETHNOGRAPHIC RESEARCH** Ethnography is the study of people and their culture. Ethnographic research, also called fieldwork, involves observation of and interaction with the persons or group being studied in the group's own environment, often for long periods of time. (*See also: Fieldwork.*)

**EXPANDED AVAILABILITY** Policy and procedure that permits individuals who have serious or life-threatening diseases for which there are no alternative therapies to have access to investigational drugs and devices that may be beneficial to them. Examples of expanded availability mechanisms include Treatment INDs, Parallel Track, and open study protocols.

**EXPEDITED REVIEW** Review of proposed research by the IRB chair or a designated voting member or group of voting members rather than by the entire IRB. Federal rules permit expedited review for certain kinds of research involving no more than minimal risk and for minor changes in approved research

**EXPERIMENTAL** Term often used to denote a therapy (drug, device, procedure) that is unproven or not yet scientifically validated with respect to safety and efficacy. A procedure may be considered "experimental" without necessarily being part of a formal study (research) to evaluate its usefulness. (*See*

*also: Research.)*

**EXPERIMENTAL STUDY** A true experimental study is one in which subjects are randomly assigned to groups that experience carefully controlled interventions manipulated by the experimenter according to a strict logic allowing causal inference about the effects of the interventions under investigation. (*See also: Quasi-Experimental Study*).

**FDA** Food and Drug Administration; an agency of the federal government established by Congress in 1912 and presently part of the Department of Health and Human Services.

**FEDERAL POLICY (THE)** The federal policy that provides regulations for the involvement of human subjects in research. The Policy applies to all research involving human subjects conducted, supported, or otherwise subject to regulation by any federal department or agency that takes appropriate administrative action to make the Policy applicable to such research. Currently, sixteen federal agencies have adopted the Federal Policy. (Also known as the "Common Rule.")

**FETAL MATERIAL** The placenta, amniotic fluid, fetal membranes, and umbilical cord.

**FETUS** The product of conception from the time of implantation until delivery. If the delivered or expelled fetus is viable, it is designated an infant [45 CFR 46.203(c)]. The term "fetus" generally refers to later phases of development; the term "embryo" is usually used for earlier phases of development. (*See also: Embryo.*)

**510(K) DEVICE** A medical device that is considered substantially equivalent to a device that was or is being legally marketed. A sponsor planning to market such a device must submit notification to the FDA 90 days in advance of placing the device on the market. If the FDA concurs with the sponsor, the device may then be marketed. 510(k) is the section of the Food, Drug and Cosmetic Act that describes premarket notification; hence the designation "510(k) device."

**FULL BOARD REVIEW** Review of proposed research at a convened meeting at which a majority of the membership of the IRB are present, including at least one member whose primary concerns are in nonscientific areas. For the research to be approved, it must receive the approval of a majority of those members present at the meeting [Federal Policy [[section]]\_\_\_\_.108].

**GENE THERAPY** The treatment of genetic disease accomplished by altering the genetic structure of either somatic (nonreproductive) or germline (reproductive) cells.

**GENERAL ASSURANCE** Obsolete term, previously used to denote an institutional assurance covering multiple research projects. (*See also: Assurance.*)

**GENERAL CONTROLS** Certain FDA statutory provisions designed to control the safety of marketed drugs and devices. The general controls include provisions on adulteration, misbranding, banned devices, good manufacturing practices, notification and record keeping, and other sections of the Medical Device Amendments to the Food, Drug and Cosmetic Act [21 U.S. Code [[section]]360(c) (Food, Drug and Cosmetic Act [[section]]513)].

**GENETIC SCREENING** Tests to identify persons who have an inherited predisposition to a certain phenotype or who are at risk of producing offspring with inherited diseases or disorders.

**GENOTYPE** The genetic constitution of an individual.

**GRANT** Financial support provided for research study designed and proposed by the principal investigator(s). The granting agency exercises no direct control over the conduct of approved research supported by a grant. (*Compare: Contract.*)

**GUARDIAN** An individual who is authorized under applicable state or local law to give permission on behalf of a child to general medical care [45 CFR 46.402(3)].

**HELSINKI DECLARATION** *See: Declaration of Helsinki.*

**HISTORICAL CONTROLS** Control subjects (followed at some time in the past or for whom data are available through records) who are used for comparison with subjects being treated concurrently. The study is considered historically controlled when the present condition of subjects is compared with their own condition on a prior regimen or treatment.

**HUMAN IN VITRO FERTILIZATION** Any fertilization involving human sperm and ova that occurs outside the human body.

**HUMAN SUBJECTS** Individuals whose physiologic or behavioral characteristics and responses are the object of study in a research project. Under the federal regulations, human subjects are defined as: living individual(s) about whom an investigator conducting research obtains: (1) data through intervention or interaction with the individual; or (2) identifiable private information [Federal Policy

**IDE** *See: Investigational Device Exemptions.*

**INCAPACITY** Refers to a person's mental status and means inability to understand information presented, to appreciate the consequences of acting (or not acting) on that information, and to make a choice. Often used as a synonym for incompetence. (*See also: Incompetence.*)

**INCOMPETENCE** Technically, a legal term meaning inability to manage one's own affairs. Often used as a synonym for incapacity. (*See also: Incapacity.*)

**IND** *See: Investigational New Drug.*

**INFORMED CONSENT** A person's voluntary agreement, based upon adequate knowledge and understanding of relevant information, to participate in research or to undergo a diagnostic, therapeutic, or preventive procedure. In giving informed consent, subjects may not waive or appear to waive any of their legal rights, or release or appear to release the investigator, the sponsor, the institution or agents thereof from liability for negligence [Federal Policy [[section]]116; 21 CFR 50.20 and 50.25].

**INSTITUTION (1)** Any public or private entity or agency (including federal, state, and local agencies)

**INSTITUTION (2)** A residential facility that provides food, shelter, and professional services (including treatment, skilled nursing, intermediate or long-term care, and custodial or residential care). Examples include general, mental, or chronic disease hospitals; inpatient community mental health centers; halfway houses and nursing homes; alcohol and drug addiction treatment centers; homes for the aged or dependent, residential schools for the mentally or physically handicapped; and homes for dependent and neglected children.

**INSTITUTIONAL REVIEW BOARD** A specially constituted review body established or designated by an entity to protect the welfare of human subjects recruited to participate in biomedical or behavioral research

**INSTITUTIONALIZED** Confined, either voluntarily or involuntarily (*e.g.*, a hospital, prison, or nursing home).

**INSTITUTIONALIZED COGNITIVELY IMPAIRED** Persons who are confined, either voluntarily or involuntarily, in a facility for the care of the mentally or otherwise disabled (*e.g.*, a psychiatric hospital, home, or school for the retarded).

**INVESTIGATIONAL DEVICE EXEMPTIONS (IDE)** Exemptions from certain regulations found in the Medical Device Amendments that allow shipment of unapproved devices for use in clinical investigations [21 CFR 812.20].

**INVESTIGATIONAL NEW DRUG OR DEVICE** A drug or device permitted by FDA to be tested in humans but not yet determined to be safe and effective for a particular use in the general population and not yet licensed for marketing.

**INVESTIGATOR** In clinical trials, an individual who actually conducts an investigation [21 CFR 312.3]. Any interventions (*e.g.*, drugs) involved in the study are administered to subjects under the immediate direction of the investigator. (*See also: Principal Investigator.*)

**IN VITRO** Literally, "in glass" or "test tube;" used to refer to processes that are carried out outside the living body, usually in the laboratory, as distinguished from *in vivo*.

**IN VIVO** Literally, "in the living body;" processes, such as the absorption of a drug by the human body, carried out in the living body rather than in a laboratory (*in vitro*).

**IRB** *See: Institutional Review Board.*

**JUSTICE** An ethical principle discussed in the *Belmont Report* requiring fairness in distribution of burdens and benefits; often expressed in terms of treating persons of similar circumstances or characteristics similarly.

**LACTATION** The period of time during which a woman is providing her breast milk to an infant or child.

**LEGALLY AUTHORIZED REPRESENTATIVE** A person authorized either by statute or by court appointment to make decisions on behalf of another person. In human subjects research, an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research [Federal Policy [[section]]\_\_\_\_.102(c)].

**LONGITUDINAL STUDY** A study designed to follow subjects forward through time.

**MASKED STUDY DESIGNS** Study designs comparing two or more interventions in which either the investigators, the subjects, or some combination thereof do not know the treatment group assignments of individual subjects. Sometimes called "blind" study designs. (*See also: Double-Masked Design; Single-Masked Design.*)

**MATURE MINOR** Someone who has not reached adulthood (as defined by state law) but who may be treated as an adult for certain purposes (*e.g.*, consenting to medical care). Note that a mature minor is not

necessarily an emancipated minor. (*See also: Emancipated Minor.*)

**MEDICAL DEVICE** A diagnostic or therapeutic article that does not achieve any of its principal intended purpose through chemical action within or on the body. Such devices include diagnostic test kits, crutches, electrodes, pacemakers, arterial grafts, intraocular lenses, and orthopedic pins or other orthopedic equipment.

**MEDICAL DEVICE AMENDMENTS (MDA)** Amendments to the Federal Food, Drug and Cosmetic Act passed in 1976 to regulate the distribution of medical devices and diagnostic products.

**MENTALLY DISABLED** *See: Cognitively Impaired.*

**METABOLISM (OF A DRUG)** The manner in which a drug is acted upon (taken up, converted to other substances, and excreted) by various organs of the body.

**MINIMAL RISK** A risk is minimal where the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater, in and of themselves, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests [Federal Policy [[section]]\_\_\_.102(i)]. For example, the risk of drawing a small amount of blood from a healthy individual for research purposes is no greater than the risk of doing so as part of routine physical examination.

The definition of minimal risk for research involving prisoners differs somewhat from that given for non-institutionalized adults. [*See* 45 CFR 46.303(d) and Guidebook Chapter 6, Section E, "Prisoners."]

**MONITORING** The collection and analysis of data as the project progresses to assure the appropriateness of the research, its design and subject protections.

**NATIONAL COMMISSION** National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. An interdisciplinary advisory body, established by Congressional legislation in 1974, which was in existence until 1978, and which issued a series of reports and recommendations on ethical issues in research and medicine, many of which are now embodied in federal regulations.

**NDA** *See: New Drug Application.*

**NEW DRUG APPLICATION** Request for FDA approval to market a new drug.

**NIAAA** National Institute on Alcohol Abuse and Alcoholism; an institute in NIH.

**NIDA** National Institute on Drug Abuse; an institute in NIH.

**NIH** National Institutes of Health: a federal agency within the Public Health Service, DHHS, comprising 21 institutes and centers. It is responsible for carrying out and supporting biomedical and behavioral research.

**NIMH** National Institute of Mental Health; an institute in NIH.

**NONAFFILIATED MEMBER** Member of an Institutional Review Board who has no ties to the parent institution, its staff, or faculty. This individual is usually from the local community (*e.g.*, minister, business person, attorney, teacher, homemaker).

**NONSIGNIFICANT RISK DEVICE** An investigational medical device that does not present significant risk to the patient. (*See also: Significant Risk Device.*)

**NONTHERAPEUTIC RESEARCH** Research that has no likelihood or intent of producing a diagnostic, preventive, or therapeutic benefit to the current subjects, although it may benefit subjects with a similar condition in the future.

**NONVIABLE FETUS** An expelled or delivered fetus which, although it is living, cannot possibly survive to the point of sustaining life independently, even with the support of available medical therapy [45 CFR 46.203 (d) and (e)]. Although it may be presumed that an expelled or delivered fetus is nonviable at a gestational age less than 20 weeks and weight less than 500 grams [*Federal Register* 40 (August 8, 1975): 33552], a specific determination as to viability must be made by a physician in each instance. (*See also: Viable Infant.*)

**NORMAL VOLUNTEERS** Volunteer subjects used to study normal physiology and behavior or who do not have the condition under study in a particular protocol, used as comparisons with subjects who do have the condition. "Normal" may not mean normal in all respects. For example, patients with broken legs (if not on medication that will affect the results) may serve as normal volunteers in studies of metabolism, cognitive development, and the like. Similarly, patients with heart disease but without diabetes may be the "normals" in a study of diabetes complicated by heart disease.

**NUREMBERG CODE** A code of research ethics developed during the trials of Nazi war criminals following World War II and widely adopted as a standard during the 1950s and 1960s for protecting human subjects.

**OFFICE FOR HUMAN RESEARCH PROTECTIONS (OHRP)** The office within the National Institutes of Health, an agency of the Public Health Service, Department of Health and Human Services, responsible for implementing DHHS regulations (45 CFR Part 46) governing research involving human subjects.

**OPEN DESIGN** An experimental design in which both the investigator(s) and the subjects know the treatment group(s) to which subjects are assigned.

**PATERNALISM** Making decisions for others against or apart from their wishes with the intent of doing them good.

**PERMISSION** The agreement of parent(s) or guardian to the participation of their child or ward in research [45 CFR 46.402(c)].

**PHARMACOLOGY** The scientific discipline that studies the action of drugs on living systems (animals or human beings).

**PHASE 1, 2, 3, 4 DRUG TRIALS** Different stages of testing drugs in humans, from first application in humans (Phase 1) through limited and broad clinical tests (Phase 3), to postmarketing studies (Phase 4).

**PHASE 1 DRUG TRIAL** Phase 1 trials include the initial introduction of an investigational new drug into humans. These studies are typically conducted with healthy volunteers; sometimes, where the drug is intended for use in patients with a particular disease, however, such patients may participate as subjects. Phase 1 trials are designed to determine the metabolic and pharmacological actions of the drug in humans, the side effects associated with increasing doses (to establish a safe dose range), and, if possible, to gain early evidence of effectiveness; they are typically closely monitored. The ultimate goal of Phase 1 trials is to obtain sufficient information about the drug's pharmacokinetics and pharmacological effects to permit the design of well-controlled, sufficiently valid Phase 2 studies. Other examples of Phase 1 studies include studies of drug metabolism, structure-activity relationships, and mechanisms of actions in humans, as well as studies in which investigational drugs are used as research tools to explore biological phenomena or disease processes. The total number of subjects involved in Phase 1 investigations is generally in the range of 20-80.

**PHASE 2 DRUG TRIAL** Phase 2 trials include controlled clinical studies conducted to evaluate the drug's effectiveness for a particular indication in patients with the disease or condition under study, and to determine the common short-term side effects and risks associated with the drug. These studies are typically well-controlled, closely monitored, and conducted with a relatively small number of patients, usually involving no more than several hundred subjects.

**PHASE 3 DRUG TRIAL** Phase 3 trials involve the administration of a new drug to a larger number of patients in different clinical settings to determine its safety, efficacy, and appropriate dosage. They are performed after preliminary evidence of effectiveness has been obtained, and are intended to gather necessary additional information about effectiveness and safety for evaluating the overall benefit-risk relationship of the drug, and to provide an adequate basis for physician labeling. In Phase 3 studies, the drug is used the way it would be administered when marketed. When these studies are completed and the sponsor believes that the drug is safe and effective under specific conditions, the sponsor applies to the FDA for approval to market the drug. Phase 3 trials usually involve several hundred to several thousand patient-subjects.

**PHASE 4 DRUG TRIAL** Concurrent with marketing approval, FDA may seek agreement from the sponsor to conduct certain post-marketing (Phase 4) studies to delineate additional information about the drug's risks, benefits, and optimal use. These studies could include, but would not be limited to, studying different doses or schedules of administration than were used in Phase 2 studies, use of the drug in other patient populations or other stages of the disease, or use of the drug over a longer period of time [21 CFR [section]]312.85].

**PHENOTYPE** The physical manifestation of a gene function.

**PHS** Public Health Service. Part of the U.S. Department of Health and Human Services, it includes FDA, NIH, CDC, SAMHSA, and HRSA.

**PLACEBO** A chemically inert substance given in the guise of medicine for its psychologically suggestive effect; used in controlled clinical trials to determine whether improvement and side effects may reflect imagination or anticipation rather than actual power of a drug.

**POSTAMENDMENTS DEVICES** Medical devices marketed after enactment of the 1976 Medical Device Amendments.

**PREAMENDMENTS DEVICES** Medical devices marketed before enactment of the 1976 Medical

Device Amendments.

**PRECLINICAL INVESTIGATIONS** Laboratory and animal studies designed to test the mechanisms, safety, and efficacy of an intervention prior to its applications to humans.

**PREDICATE DEVICES** Currently legally marketed devices to which new devices may be found substantially equivalent under the 510(k) process.

**PREGNANCY** The period of time from confirmation of implantation of a fertilized egg within the uterus until the fetus has entirely left the uterus (*i.e.*, has been delivered). Implantation is confirmed through a presumptive sign of pregnancy such as missed menses or a positive pregnancy test [45 CFR 46.203(b)]. This "confirmation" may be in error, but, for research purposes, investigators would presume that a living fetus was present until evidence to the contrary was clear. Although fertilization occurs a week or more before implantation, the current inability to detect the fertilization event or the presence of a newly fertilized egg makes a definition of pregnancy based on implantation necessary.

**PREMARKET APPROVAL** Process of scientific and regulatory review by the FDA to ensure the safety and effectiveness of Class III devices.

**PRESIDENT'S COMMISSION** President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. An interdisciplinary advisory group, established by congressional legislation in 1978, which was in existence until 1983, and which issued reports on ethical problems in health care and in research involving human subjects.

**PRINCIPAL INVESTIGATOR** The scientist or scholar with primary responsibility for the design and conduct of a research project. (*See also: Investigator.*)

**PRISONER** An individual involuntarily confined in a penal institution, including persons: (1) sentenced under a criminal or civil statute; (2) detained pending arraignment, trial, or sentencing; and (3) detained in other facilities (*e.g.*, for drug detoxification or treatment of alcoholism) under statutes or commitment procedures providing such alternatives to criminal prosecution or incarceration in a penal institution [45 CFR 46.303(c)].

**PRIVACY** Control over the extent, timing, and circumstances of sharing oneself (physically, behaviorally, or intellectually) with others.

**PROBAND** The person whose case serves as the stimulus for the study of other members of the family to identify the possible genetic factors involved in a given disease, condition, or characteristic.

**PROPHYLACTIC** Preventive or protective; a drug, vaccine, regimen, or device designed to prevent, or provide protection against, a given disease or disorder.

**PROSPECTIVE STUDIES** Studies designed to observe outcomes or events that occur subsequent to the identification of the group of subjects to be studied. Prospective studies need not involve manipulation or intervention but may be purely observational or involve only the collection of data.

**PROTOCOL** The formal design or plan of an experiment or research activity; specifically, the plan submitted to an IRB for review and to an agency for research support. The protocol includes a description of the research design or methodology to be employed, the eligibility requirements for prospective subjects and controls, the treatment regimen(s), and the proposed methods of analysis that will be performed on the collected data.

**PROTOCOL DEVIATIONS:** violations and deviations occur when there is a variance in a research study between the protocol that has been reviewed and approved by the IRB and the actual performance within the research study.

**PURITY** The relative absence of extraneous matter in a drug or vaccine that may or may not be harmful to the recipient or deleterious to the product.

**QUASI-EXPERIMENTAL STUDY** A study that is similar to a true experimental study except that it lacks random assignments of subjects to treatment groups. (*See also: Experimental Study.*)

**RADIOACTIVE DRUG** Any substance defined as a drug in [[section]]201(b)(1) of the Federal Food, Drug and Cosmetic Act that exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons [21 CFR 310.3(n)]. Included are any non-radioactive reagent kit or nuclide generator that is intended to be used in the preparation of a radioactive drug and "radioactive biological products," as defined in 21 CFR 600.3(ee). Drugs such as carbon-containing compounds or potassium-containing salts containing trace quantities of naturally occurring radionuclides are not considered radioactive drugs.

**RADIOACTIVE DRUG RESEARCH COMMITTEE (RDRC)** An institutional committee responsible

for the use of radioactive drugs in human subjects for research purposes. Research involving human subjects that proposes to use radioactive drugs must meet various FDA requirements, including limitations on the pharmacological dose and the radiation dose. Furthermore, the exposure to radiation must be justified by the quality of the study and the importance of the information it seeks to obtain. The committee is also responsible for continuing review of the drug use to ensure that the research continues to comply with FDA requirements, including reporting obligations. The committee must include experts in nuclear medicine and the use of radioactive drugs, as well as other medical and scientific members [21 CFR 36.1].

**RADIOPAQUE CONTRAST AGENTS** Materials that stop or attenuate radiation that is passed through the body, creating an outline on film of the organ(s) being examined. Contrast agents, sometimes called "dyes," do not contain radioisotopes. When such agents are used, exposure to radiation results only from the X-ray equipment used in the examination. The chemical structure of radiopaque contrast agents can produce a variety of adverse reactions, some of which may be severe -- and possibly life-threatening -- in certain individuals.

**RADIOPHARMACEUTICALS** Drugs (compounds or materials) that may be labeled or tagged with a radioisotope. These materials are largely physiological or sub-pharmacological in action, and, in many cases, function much like materials found in the body. The principal risk associated with these materials is the consequent radiation exposure to the body or to specific organ systems when they are injected into the body.

**RANDOM, RANDOM ASSIGNMENT, RANDOMIZATION, RANDOMIZED** Assignment of subjects to different treatments, interventions, or conditions according to chance rather than systematically (e.g., as dictated by the standard or usual response to their condition, history, or prognosis, or according to demographic characteristics). Random assignment of subjects to conditions is an essential element of experimental research because it makes more likely the probability that differences observed between subject groups are the result of the experimental intervention.

**RECOMBINANT DNA TECHNOLOGY** "The ability to chop up DNA, the stuff of which genes are made, and move the pieces, [which] permits the direct examination of the human genome," and the identification of the genetic components of a wide variety of disorders [Holtzman (1989), p. 1]. Recombinant DNA technology is also used to develop diagnostic screens and tests, as well as drugs and biologics for treating diseases with genetic components. *See* Guidebook Chapter 5, Section H, "Human Genetic Research."

**REM** Acronym for **Roentgen Equivalent in Man**; the unit of measurement for a dose of an ionizing radiation that produces the same biological effect as a unit of absorbed dose (1 rad) of ordinary X-rays. One millirem is equal to 1/1000 of a rem.

**REMISSION** A period in which the signs and symptoms of a disease are diminished or in abeyance. The term "remission" is used when one cannot say with confidence that the disease has been cured.

**REMUNERATION** Payment for participation in research. (NOTE: It is wise to confine use of the term "compensation" to payment or provision of care for research-related injuries.) (*Compare: Compensation.*)

**RESEARCH** A systematic investigation (i.e., the gathering and analysis of information) designed to develop or contribute to generalizable knowledge [Federal Policy [[section]]\_\_\_.102(d)].

**RESEARCH MISCONDUCT** is defined as: Fabrication, falsification or plagiarism in proposing, performing, or reviewing research, or in reporting research results. Fabrication is making up data or results and recording or reporting them. Falsification is manipulating research materials, equipment, or processes, or changing or omitting data or results such that the research is not accurately represented in the research record. Plagiarism is the appropriation of another person's ideas, processes, results, or words without giving appropriate credit. Research misconduct does not include honest error or differences of opinion. 42 CFR Part 93, Sec. 93.103

**RESPECT FOR PERSONS** An ethical principle discussed in the *Belmont Report* requiring that individual autonomy be respected and that persons with diminished autonomy be protected.

**RETROSPECTIVE STUDIES** Research conducted by reviewing records from the past (e.g., birth and death certificates, medical records, school records, or employment records) or by obtaining information about past events elicited through interviews or surveys. Case control studies are an example of this type of research.

**REVIEW (OF RESEARCH)** The concurrent oversight of research on a periodic basis by an IRB. In

addition to the at least annual reviews mandated by the federal regulations, reviews may, if deemed appropriate, also be conducted on a continuous or periodic basis [Federal Policy [[section]]\_\_\_\_.108(e)].

**RISK** The probability of harm or injury (physical, psychological, social, or economic) occurring as a result of participation in a research study. Both the probability and magnitude of possible harm may vary from minimal to significant. Federal regulations define only "minimal risk." (*See also: Minimal Risk.*)

**SCIENTIFIC REVIEW GROUP** A group of highly regarded experts in a given field, convened by NIH to advise NIH on the scientific merit of applications for research grants and contracts. Scientific review groups are also required to review the ethical aspects of proposed involvement of human subjects. Various kinds of scientific review groups exist, and are known by different names in different institutes of the NIH (*e.g.*, Study Sections, Initial Review Groups, Contract Review Committees, or Technical Evaluation Committees).

**SECRETARY** A U.S. Cabinet Officer. In the context of DHHS-conducted or -supported research, usually refers to the Secretary of Health and Human Services.

**SIGNIFICANT RISK DEVICE** An investigational medical device that presents a potential for serious risk to the health, safety, or welfare of the subject.

**SINGLE-MASKED DESIGN** Typically, a study design in which the investigator, but not the subject, knows the identity of the treatment assignment. Occasionally the subject, but not the investigator, knows the assignment. Sometimes called "single-blind design."

**SITE VISIT** A visit by agency officials, representatives, or consultants to the location of a research activity to assess the adequacy of IRB protection of human subjects or the capability of personnel to conduct the research.

**SOCIAL EXPERIMENTATION** Systematic manipulation of, or experimentation in, social or economic systems; used in planning public policy.

**SPONSOR (OF A DRUG TRIAL)** A person or entity that initiates a clinical investigation of a drug -- usually the drug manufacturer or research institution that developed the drug. The sponsor does not actually conduct the investigation, but rather distributes the new drug to investigators and physicians for clinical trials. The drug is administered to subjects under the immediate direction of an investigator who is not also a sponsor. A clinical investigator may, however, serve as a sponsor-investigator. The sponsor assumes responsibility for investigating the new drug, including responsibility for compliance with applicable laws and regulations. The sponsor, for example, is responsible for obtaining FDA approval to conduct a trial and for reporting the results of the trial to the FDA.

**SPONSOR-INVESTIGATOR** An individual who both initiates and actually conducts, alone or with others, a clinical investigation. Corporations, agencies, or other institutions do not qualify as sponsor-investigators.

**STATISTICAL SIGNIFICANCE** A determination of the probability of obtaining the particular distribution of the data on the assumption that the null hypothesis is true. Or, more simply put, the probability of coming to a false positive conclusion. [*See McLarty (1987), p. 2.*] If the probability is less than or equal to a predetermined value (*e.g.*, 0.05 or 0.01), then the null hypothesis is rejected at that significance level (0.05 or 0.01).

**STERILITY (1)** The absence of viable contaminating microorganisms; aseptic state.

**STERILITY (2)** The inability to procreate; the inability to conceive or induce conception.

**SUBJECTS (HUMAN)** *See: Human Subjects.*

**SURVEYS** Studies designed to obtain information from a large number of respondents through written questionnaires, telephone interviews, door-to-door canvassing, or similar procedures.

**THERAPEUTIC INTENT** The research physician's intent to provide some benefit to improving a subject's condition (*e.g.*, prolongation of life, shrinkage of tumor, or improved quality of life, even though cure or dramatic improvement cannot necessarily be effected.) This term is sometimes associated with Phase 1 drug studies in which potentially toxic drugs are given to an individual with the hope of inducing some improvement in the patient's condition as well as assessing the safety and pharmacology of a drug.

**THERAPY** Treatment intended and expected to alleviate a disease or disorder.

**UNIFORM ANATOMICAL GIFT ACT** Legislation adopted by all 50 States and the District of Columbia that indicates procedures for donation of all or part of a decedent's body for such activities as medical education, scientific research, and organ transplantation.

**VACCINE** A biologic product generally made from an infectious agent or its components --a virus, bacterium, or other microorganism -- that is killed (inactive) or live-attenuated (active, although

weakened). Vaccines may also be biochemically synthesized or made through recombinant DNA techniques.

**VARIABLE (NOUN)** An element or factor that the research is designed to study, either as an experimental intervention or a possible outcome (or factor *affecting* the outcome) of that intervention.

**VIABLE INFANT** When referring to a delivered or expelled fetus, the term "viable infant" means likely to survive to the point of sustaining life independently, given the benefit of available medical therapy [45 CFR 46.203(d)]. This judgment is made by a physician. In accordance with DHHS regulations, the Secretary, HHS, may publish guidelines to assist in the determination of viability. Such guidelines were published in 1975, and specify an estimated gestational age of 20 weeks or more and a body weight of 500 grams or more as indices of fetal viability [*Federal Register* 40 (August 8, 1975): 33552]. These indices depend on the state of present technology and may be revised periodically. (*See also: Nonviable Fetus.*)

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

**VII. RELATED DOCUMENTS**

Investigator Handbook (attached), Investigational Drugs Policy and Procedures (pharmacy), Research Misconduct NH-LD-AD-210, NH policy: Use or Disclosure of Patient Health Information in Research,

**VIII. REFERENCES**

VI. 45 CFR 46; 21 CFR 56; 21 CFR 50; FDA Information Sheets 1998 pages 1, 8; 21 CFR 312, 21 CFR Parts 812 and 814, FDA Information Sheets 7/18/06, "Guidance for Industry and FDA Staff - Humanitarian Device Exemption (HDE) Regulation: Questions and Answers" 42 CFR Part 93, Sec. 93.103 ; NH-LD-AD-210, ICH guidelines for GCP E6

**IX. SUBMITTED BY**

IRB Chair, Elms Allen, MD, IRB Manager, Beth Cirillo, Institutional Review Board, Melissa Phipps, Asst General Counsel

**X. KEY WORDS**

Institutional Review Board, IRB, Human Research, Protections, Study Protocol, Principal Investigator, Clinical Trial

**XI. INITIAL EFFECTIVE DATE** 01 MAR 2001  
**DATE REVISED** MAY 2008  
**DATE REVIEWED** 04 DEC 2003

**PROCEDURE SIGNATURE SHEET (one copy only to be maintained by author)**

<b>Company / Facility(s)</b>	Forsyth Medical Center
<b>Department</b>	Medical Staff Services
<b>Procedure</b>	Formation and Operation of an Institutional Review Board
<b>Action</b>	Revised

**PROCEDURE APPROVED BY:**

<b>Title</b>	<b>Approved By</b>	<b>Signature</b>	<b>Date</b>
Sr VP Medical Staff Services	Elms Allen, MD		5/8/08
President Medical Dental Staff	Nick Chrysson, MD		5/8/08

**COMMITTEES APPROVED BY:**

<b>Committee</b>	<b>Chairperson/Designee</b>	<b>Date</b>
Forsyth Medical Center IRB	Elms Allen, MD	5/8/08
NH Patient Rights Committee	Reba Teeter	5/8/08

**DATES OF APPROVAL:**

<b>Date Revised</b>	May 2008
<b>Date to be Reviewed</b>	May 2011

**TABLE 1 – PEDIATRIC RISK LEVEL**

Risk of Harm Category	Requirements
<b>Level 1 – No greater than minimal risk</b>	Assent* of child and permission** of at least one parent/guardian
<b>Level 2 – Greater than minimal risk and prospect of direct benefit to the child</b>	<ul style="list-style-type: none"> <li>● Assent* of child and permission** of at least one parent/guardian</li> <li>● Anticipated benefit justifies the risk</li> <li>● Anticipated benefit is at least as favorable as that of alternative approaches</li> </ul>
<b>Level 3 – Greater than minimal risk and no prospect of direct benefit to the child, but likely to yield generalizable knowledge about the child’s disorder or condition</b>	<ul style="list-style-type: none"> <li>● Assent* of child and permission** of <b>both</b> parents/guardians</li> <li>● Only a minor increase over minimal risk</li> <li>● Likely to yield generalizable knowledge about the child’s disorder or condition that is of vital importance for the understanding or amelioration of the disorder or condition</li> <li>● the intervention or procedure presents experiences to the child that are reasonably commensurate with those in the child’s actual or expected medical, dental, psychological, social or educational situations</li> </ul>
<b>Level 4 – Research not otherwise approvable (does not meet the requirements of Levels 1, 2 or 3)</b>	<ul style="list-style-type: none"> <li>● Assent* of child and permission** of <b>both</b> parents/guardians</li> <li>● IRB finds that the research presents a reasonable opportunity to further the understanding, prevention or alleviation of a serious problem affecting the health or welfare of children</li> <li>● the FDA Commissioner approves the research in accordance with federal regulations</li> </ul>

\*Assent may be waived by the IRB

\*\* Permission = parental informed consent