Overview: This booklet is designed to help investigators better meet their obligations for conducting human subject research by clarifying their responsibility (1) to supervise a clinical study in which some study tasks are delegated to employees or colleagues of the investigator or other third parties, and (2) to protect the rights, safety and welfare of study subjects.

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Introduction

This booklet is intended for use by individuals who conduct clinical investigations involving human subjects at Baptist Health South Florida. These studies include, but are not limited to, the investigation of pharmaceutical agents, biological products and medical devices.

The booklet is designed to help investigators better meet their obligations for conducting human subject research by clarifying their responsibility (1) to supervise a clinical study in which some study tasks are delegated to employees or colleagues of the investigator or other third parties and (2) to protect the rights, safety and welfare of study subjects.

Upon completion of this booklet, participants will be better able to:

- Describe the history and importance of the protection of human subjects.
- Explain why additional protections are needed for vulnerable populations.
- Delineate the appropriate procedures for recruiting research participants.
- Implement the requirements and the processes for obtaining informed consent based on national evidence-based guidelines and the Baptist Health IRB policies and procedures.
- Recognize the importance of study design in the protection of research participants.
- Explain the responsibilities of a principal investigator.

PART I – HISTORY

The protection of human subjects in research begins with the Nuremberg Code, developed for the Nuremberg Military Tribunal as standards by which to judge human experimentation. The Code captures many of what are now taken to be the basic principles governing the ethical conduct of research involving human subjects. The first provision of the Code states that "the voluntary consent of the human subject is absolutely essential." The Code goes on to provide the details implied by such a requirement: capacity to consent, freedom from coercion, and comprehension of the risks and benefits involved. Other provisions require the minimization of risk and harm, a favorable risk/benefit ratio, qualified investigators using appropriate research designs, and freedom for the subject to withdraw at any time. Recommendations for the regulations for the protection of human subjects in research were also made by the World Medical Association in its Declaration of Helsinki: Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects, first adopted by the 18th World Medical Assembly in Helsinki, Finland, in 1964, and subsequently revised by the 29th World Medical Assembly in Tokyo, Japan, in 1975, and by the 41st World Medical Assembly in Hong Kong in 1989. The Declaration of Helsinki further distinguishes therapeutic from non-therapeutic research.

The Department of Health, Education and Welfare (HEW) regulations protecting human subjects first became effective on May 30, 1974. The regulations established the Institutional Review Board (IRB) as one mechanism through which human subjects would be protected.

In July of 1974, the National Research Act established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Commission issued reports and recommendations for the conduct of biomedical and behavioral research involving human subjects and recommended guidelines to ensure that research is conducted in accordance with those principles. The Commission required that the
guidelines apply to research conducted or supported by HEW. The Commission’s report setting forth the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects is titled *The Belmont Report*.

The Belmont Report identified three principles essential to the ethical conduct of research with humans:

- Respect for persons
- Beneficence
- Justice

➤ Respect for Persons

The principle of respect for persons can be broken down into two basic ideas:

1. Individuals should be treated as autonomous agents.
2. Persons with diminished autonomy are entitled to additional protections.

The principle is applied in the consent process. The challenges in applying the Belmont principle of respect for persons are in:

- Making sure that potential participants comprehend the risks and potential benefits of participating in research.
- Avoiding influencing potential participants’ decisions either through explicit or implied threats (coercion) or through excessive compensation (undue influence).

➤ Beneficence

Two general rules have been articulated as complementary expressions of beneficent actions:

- Do no harm.
- Maximize possible benefits and minimize possible risks.

The principle is applied in risk/benefit assessment. The challenge inherent in applying the Belmont principle of beneficence is how to determine when potential benefits outweigh considerations of risks and vice versa.

➤ Justice

Justice requires that individuals and groups be treated fairly and equitably in terms of bearing the burdens and receiving the benefits of research.

The principle is applied in the selection of research subjects. The principle of justice may arise in decisions about inclusion and exclusion criteria for participation in research and require investigators to question whether groups are considered for inclusion simply because of their availability, their compromised position or their vulnerability – rather than for reasons directly related to the problem being studied.

In 1981, the Department of Health and Human Services (HHS), formally known as HEW, and the Food & Drug Administration (FDA) published unified regulations that were based on the Belmont Principles.

In 1991, the Common Rule was designed to make uniform the human subjects protection system in all relevant 16 federal agencies and departments.
Under the direction of the HHS, institutions receiving federal grants or contracts must file a Federal Wide Assurance (FWA) with the Office for Human Research Protections (OHRP). The OHRP provides regulations, guidelines and education to IRBs. In the FWA, the institution agrees to apply the federal regulations and ethical principles of the Belmont Report. Institutions must periodically reapply for and negotiate the terms of their FWA.

HHS regulation for the Protection of Human Subjects [45 CFR 46] defines a human subject as follows:

*Human subject* means a living individual about whom an investigator (whether professional or student) conducting research obtains

1. Data through intervention or interaction with the individual, or
2. Identifiable private information.

DHHS regulation for the Protection of Human Subjects [45 CFR 46] defines research as follows:

*Research* means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.

### PART II – VULNERABLE SUBJECTS

The federal regulations require that IRBs give special consideration to protecting the welfare of particularly vulnerable subjects, such as children, prisoners, pregnant women, mentally disabled persons or economically or educationally disadvantaged persons.

The HHS regulations set forth specific provisions on research involving fetuses, pregnant women [45 CFR 46 Subpart B]; prisoners [45 CFR 46 Subpart C]; and children [45 CFR 46 Subpart D]. These regulations allow IRBs to approve research that is of minimal risk or that will benefit the subjects directly. Studies that present significantly greater than minimal risk without direct benefit must be reviewed and approved by HHS in consultation with appropriate experts.

- Research involving fetuses and pregnant women [45 CFR 46 Subpart B]

The IRB may approve research directed toward the fetus in utero if: (1) the purpose of the research is to meet the health needs of the fetus and is conducted in a way that will minimize risk (e.g., a new technique for fetal transfusion for Rh incompatibility); or (2) the research poses no more than minimal risk to the fetus (e.g., minor changes in maternal diet or use of ultrasonography) and the purpose of the activity is the development of important biomedical knowledge that is unobtainable by other means.

If an ex utero fetus is judged viable (i.e., likely to survive to the point of sustaining life independently, given the benefit of available medical therapy), it is then called an infant. At this point, the IRB must be guided by regulations and policies dealing with children. Research activities involving the dead fetus, macerated fetal material, or cells, tissue or organs excised from a dead fetus are governed by state laws and regulations.

Any study in which women of childbearing potential are possible subjects may inadvertently include pregnant women. HHS regulations require that, when appropriate, subjects be provided a “statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable” as part of the informed consent process. Furthermore, where appropriate, subjects should be advised to notify the investigator immediately should they become pregnant. In some instances there may be potential risk sufficient to justify requiring that pregnant women be specifically excluded from the research.
The primary requirement for approval of research in this category is the IRB determination that the risk to the fetus is "minimal." The definition suggests that if the estimated risk to the fetus is no more than that from established procedures routinely used in an uncomplicated pregnancy or in a pregnancy with complications comparable to those being studied, the risk is considered minimal. If the IRB cannot conclude that fetal risk is minimal, it may conditionally approve the research, subject to review and approval by the HHS secretary.

- Research involving prisoners [45 CFR 46 Subpart C]

HHS regulations have special requirements regarding the membership of the IRB that reviews research involving prisoners. At least one member of the IRB must be a prisoner or a prisoner representative with the appropriate background and experience to serve in that capacity. A majority of IRB members (exclusive of prison members), must have no other association, apart from IRB membership, with the prison(s) involved.

Only certain kinds of research conducted or supported by HHS may involve prisoners as subjects: (1) studies (involving no more than minimal risk or inconvenience) of the possible causes, effects and processes of incarceration and criminal behavior; (2) studies (involving no more than minimal risk or inconvenience) of prisons as institutional structures or of prisoners as incarcerated persons; (3) research on particular conditions affecting prisoners as a class, and (4) research involving a therapy likely to benefit the prisoner subject. If the therapeutic research also involves non-therapeutic research with a control group, HHS must also consult with appropriate experts.

The IRB has additional responsibilities when reviewing research involving prisoners [45 CFR 46.305].

- It must determine whether any advantages the prisoners may obtain through participation in the research are of sufficient magnitude to impair the inmates' ability to choose to participate, given the institutional context of limited choice (advantage as compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison).
- It must decide if the risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers.
- It must ensure that the procedures for selecting subjects are fair and immune from arbitrary intervention by prison authorities or prisoners.
- There must be adequate assurances that parole boards will not take a prisoner's participation in research into account when making parole decisions, and each prisoner must be clearly informed in advance that participation will have no effect on his or her parole.
- The research institution must thereafter certify to the DHHS Secretary that these special responsibilities have been fulfilled.

- Research involving children [45 CFR 46 Subpart D]

The federal regulations require IRBs to classify research involving children into one of four categories and to document their discussions of the risks and benefits of the research study. The four categories of research involving children that may be approved by IRBs, based on degree of risk and benefit to individual subjects, are as follows:

1. Research not involving greater than minimal risk.

2. Research involving greater than minimal risk, but presenting the prospect of direct benefit to an individual subject. Research in this category is approvable provided: (a) the risk is justified by the anticipated benefit to the subject; and (b) the relationship of risk to benefit is at least as favorable as any available alternative approach.
3. Research involving greater than minimal risk with no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition. Research in this category is approvable provided: (a) the risk represents a minor increase over minimal risk; (b) the intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social or educational settings; and (c) the intervention or procedure is likely to yield generalizable knowledge about the subject's disorder or condition that is of vital importance for the understanding or amelioration of the subject's disorder or condition.

4. Research that is not otherwise approvable, but that presents an opportunity to understand, prevent or alleviate a serious problem affecting the health or welfare of children. Research that is not approvable under 45 CFR 46.404, 46.405, or 46.406 may be conducted or funded by HHS provided that the IRB and the secretary, after consultation with a panel of experts, find that the research presents a reasonable opportunity to further the understanding, prevention or alleviation of a significant problem affecting the health and welfare of children. The panel of experts must also find that the research will be conducted in accordance with sound ethical principles.

In all cases, the IRB must determine that adequate provisions have been made for soliciting the assent of children and the permission of their parents or guardians.

PART III – SELECTION OF SUBJECTS

IRBs are responsible for ensuring the equitable selection of research subjects. In fulfilling this responsibility, IRBs must review the methods that investigators use to recruit subjects. The requirement for an equitable selection of subjects helps ensure that the burdens and benefits of research will be fairly distributed.

If an investigator also serves as a patient's primary physician, he or she may feel obliged to participate in the research out of a desire to please, gratitude, or fear that failure to do so will result in hostility or abandonment. Patients who are dependent upon a particular facility for their care may feel that they will be treated less well or with less favor if they refuse to participate in research.

With these caveats in mind, investigators must be careful not to overprotect vulnerable populations so that they are excluded from participating in research in which they wish to participate, particularly if the research involves therapies for conditions with no available treatments.

Just as the inclusion of disproportionate numbers of racial or ethnic minorities in research studies might overburden these groups without affording them the benefits that will result from the research, so will underrepresentation of these groups in study populations ensure that they will not benefit from the research.

The National Commission for the Protection of Human Subjects recommends that, as a matter of social justice, there should be an order of preference in the selection of classes of subjects: adults before children, competent individuals before incompetent individuals, and non-institutionalized persons before institutionalized persons. In addition, the Commission believes that those who are already burdened (e.g., by disabilities or institutionalization) should not be asked to accept the burdens of research unless other appropriate subjects cannot be found (i.e., if the research concerns their particular disability or circumstance).

When determining whether the burdens of research are being distributed equitably, it is appropriate for the IRB to consider more than the risks associated with the research procedures. It may be appropriate to consider such things as inconvenience (i.e., the time required, travel involved, restrictions on diet or other activities), discomfort and embarrassment as burdens of participating in research.
Potential subjects may be identified through records maintained at hospitals or physicians' private offices. If potential subjects are identified through medical records, log books, physicians' records or other records that are not public documents, the IRB must make certain that the following conditions have been met: (1) the investigator is allowed access to such records by the institution or the physician; and (2) responsibility for confidentiality and protection of privacy is met.

For a hospital-based study, the IRB may require that a potential subject's physician give approval before the subject is contacted, particularly when there may be medical or emotional contraindications to participation. If the subject is in the hospital, someone on the hospital staff who provides direct patient care to that patient may inform the patient that he or she is going to be invited to participate in a study, or, more often, an interviewer may approach the subject directly after consultation with his or her physician.

If the subject has left the hospital, various options may be considered. For instance, after approval from the physician, the investigator may send a letter describing the purpose of the study and requesting that the subject return a postcard indicating whether he or she would like to participate.

Another approach that is often used is for the patient's physician to send a letter informing the subject about the study and inviting the patient to participate. This method may work well if the study is being undertaken by a relatively small number of physicians who are willing to cooperate with the investigator. Response rates are likely to be high, since the subject often considers it significant that the letter has come from his or her own physician. IRBs should consider whether use of this method will subject potential participants to coercion or undue influence.

PART IV – INFORMED CONSENT

Informed consent is one of the primary ethical requirements for research with human subjects; it reflects the basic principal of respect for persons. Informed consent ensures that prospective research subjects will understand the nature of the research and can knowledgeably and voluntarily decide whether or not to participate.

Informed consent is an ongoing conversation between the research subject and the researchers. It begins before written consent is given and continues until the end of the research subjects’ involvement in the study.

Because obtaining informed consent is an educational process, the investigator should consider the proposed subject population, the type of information to be conveyed, and the circumstances under which the consent process will take place (e.g., manner, timing, place, personnel involved).

The investigator may use the following materials for the consent process (these require IRB approval):

- pamphlets or other reading materials
- instruction sheets
- charts or diagrams
- audio or visual presentations
- Internet information

The goals of the informed consent process are to:

- Give the subject information about the research.
- Make sure the subject has time to consider all options.
- Answer all of the subject’s questions before the decision is made.
- Make sure that all information is understood by the subject.
- Continue to inform the subject throughout the research study.
continue to reaffirm the subject's consent to participate throughout the research study.

Investigators must obtain written consent, unless waived by the IRB, prior to the initiation of any study-specific procedure. Consent must be obtained only under circumstances that provide the prospective subject sufficient opportunity to consider whether or not to participate, and minimize the possibility of coercion or undue influence. The information that is given to the subject must be written in language that is understandable to the subject. Only those individuals listed in the IRB Application and approved by the IRB can obtain consent.

**Required elements of the consent form:**

Unless otherwise authorized by the IRB, research investigators must provide a written consent form that incorporates the following information, in understandable language, to each research subject:

1. A statement that the study involves research.
2. An explanation of the purpose of the research.
3. The number of subjects who will be participating at the Baptist Health entity.
4. The number of centers that will be participating in the research.
5. How long the study will last and an estimate of the total duration of the subjects’ participation in the research.
6. A description of the study procedures.
7. A description of those procedures that are standards of care and those that are experimental.
8. A description of any risks or discomforts to the subject. For drug and device studies, the list of risks must be categorized as common, less common and rare.
9. A description of any benefits to the subject or to others (no benefits may be guaranteed).
10. A description of alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
11. A description of any payments or compensation that will be provided for participating in the study.
12. A statement describing the extent to which confidentiality of records identifying the subject will be maintained.
13. A statement describing who will have access to the study records and if the patient’s medical records will be reviewed and duplicated.
14. A statement that the study records may be inspected and who will inspect these records.
15. A statement of any additional costs to the subject that may result from participation in the study.
16. Whom to contact in the event of a research-related injury to the subject.
17. An explanation as to whether medical treatment is available if injury occurs, and, if so, who is responsible for payment, and where further information may be obtained.
18. A statement that participation is voluntary.
19. A statement that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled.
20. A statement that the subject may discontinue participation, without providing a reason or explanation, at any time without penalty or loss of benefits to which the subject is otherwise entitled.
21. The consequences of a subject’s decision to withdraw from the research and procedures for orderly termination of participation by the subject.
22. Anticipated circumstances under which the subject’s participation may be terminated by the investigator without regard to the subject’s consent.
23. A statement that significant new findings developed during the course of the research which may relate to the subject’s willingness to continue participation will be provided to the subject.
24. An explanation of whom to contact for answers to pertinent questions about the study.
25. An explanation of whom to contact for questions about their rights as research subjects.
26. Include appropriate signature and date lines. Include a line for the subject to print his/her name.
27. Include a signature and date line for the person obtaining consent to sign. Include a line for the person obtaining consent to print his/her name.
28. Include a signature and date line for the witness, if applicable. Include a line for the witness to print his/her name.

29. Where applicable, include the Physician Certification statement.

30. Where applicable, include a signature and date line for the healthcare surrogate, as well as a line for the healthcare surrogate to print his/her name.

**Documentation of consent form:**

Study subjects must sign the IRB-approved consent form. The IRB approved consent form must have the Baptist Health IRB approval and expiration date. The consent form must have all the required signatures and dates. Subjects must receive a copy of the consent form and the original must be kept in the investigator’s study records.

Research trials conducted with hospitalized patients or patients who have services provided by any of the Baptist Health entities must have a research barcode label affixed to the bottom of each page of the consent form. A copy of the signed consent form, with the barcode label, must be placed in the patient’s medical records. The original signed copy is kept in the regulatory investigator’s research file (regulatory binder).

**Exceptions:**

The IRB may approve a consent form that does not include, or that alters, some or all of the elements of informed consent, provided the IRB finds and documents that the protocol meets specific regulatory requirements.

**Waiver of informed consent:**

The IRB may waive the requirements to obtain informed consent, provided the Investigator justifies to the IRB:

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

**FDA exceptions from informed consent requirements:**

Below are the FDA Sec. 50.23 exceptions from obtaining informed consent:

(a) The obtaining of informed consent shall be deemed feasible unless, before use of the test article (except as provided in paragraph (b) of this section), both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following:

1. The human subject is confronted by a life-threatening situation necessitating the use of the test article.
2. Informed consent cannot be obtained from the subject because of an inability to communicate with, or obtain legally effective consent from, the subject.
3. Time is not sufficient to obtain consent from the subject’s legal representative.
4. There is available no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject.
(b) If immediate use of the test article is, in the investigator's opinion, required to preserve the life of the subject, and time is not sufficient to obtain the independent determination required in paragraph (a) of this section in advance of using the test article, the determinations of the clinical investigator shall be made and, within five working days after the use of the article, be reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.

(c) The documentation required in paragraph (a) or (b) of this section shall be submitted to the IRB within five working days after the use of the test article.

Assent for children:

The age of majority in Florida is 18. For subjects under 18 years of age, consent must be obtained from the parent or court-appointed legal guardian. A court-appointed legal guardian must obtain court approval for participation in research studies.

- Only parental consent is required for ages 6 and under.
- Parental consent and an assent statement are required for ages 7-12.
- Parental consent and a youth assent form may be required for those ages 13 through 17.

Non-English-speaking subjects:

If it's anticipated that non-English-speaking subjects will participate in the study, the investigator must submit a written translated consent form. The translation must correspond to the IRB-approved consent form version.

If a non-English-speaking subject is not anticipated but wishes to participate in the study, the oral presentation of the consent form in conjunction with a short form written document (stating that the elements of consent have been presented orally) may be given. The oral presentation and the short form should be in a language understandable to the subject. A witness to the oral presentation is required. The translator may serve as the witness.

At the time of consent, (1) the short form should be signed by the participant (or the participant’s legally authorized representative); (2) the IRB consent form should be signed by the person obtaining consent as authorized under the protocol; and (3) the short form and the consent form should be signed by the witness/translator.

Illiterate English-speaking subjects:

A person who speaks and understands English but does not read and write it can be enrolled in a study by "making their mark" on the consent form, when consistent with applicable state law.

Subjects who are physically unable to talk or write:

A person who can understand and comprehend English but is physically unable to talk or write can be entered into a study if he or she is competent and able to indicate approval or disapproval by other means. If (1) the person retains the ability to understand the concepts of the study and evaluate the risk and benefit of being in the study when it is explained verbally (still competent) and (2) is able to indicate approval or disapproval, he or she may be entered into the study. The consent form should document the method used for communication
with the prospective subject and the specific means by which the prospective subject communicated agreement to participate in the study. An impartial third party should witness the entire consent process and sign the consent document. A videotape recording of the consent interview is recommended.

PART V – STUDY DESIGN

- **Record review**
  A study may involve only the use of existing public or privately held records. In such a case, the IRB could exempt the study from review, give it expedited review, or require that it be sent to full board review, depending on the nature of the study.

  Federal regulations allow IRBs to provide expedited review if the research presents no more than minimal risk and it must qualify under one or more of the categories approved by the DHHS. For example, if a researcher wanted to learn about risk factors (e.g., smoking habits, industrial employment or family history) related to cancer, he or she might start with medical records. This research may qualify for expedited review if the records preexist the start of the research project and if the investigator records the information in such a manner that subjects cannot be identified directly or through identifiers. The research would require IRB review to ensure that, among other things, procedures for protecting privacy and confidentiality are adequate. The investigator studying cancer risk factors may propose to go on to contact the subjects (if still living) or family members (if the subject is deceased) to gather additional information. This would require full board review.

- **Surveys, questionnaires, interviews**
  Research solely involving surveys, questionnaires or interview procedures is expedited unless the information obtained is recorded in such a manner that the subjects can be identified, and the information obtained could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability or reputation.

- **Epidemiologic studies**
  Epidemiologic studies often use sensitive private documents, such as medical records, and link them with other data, such as surveys or interviews. Epidemiologic studies do present significant problems regarding privacy and confidentiality.

  Investigators must ensure that they take adequate steps to preserve the confidentiality of the data they collect, requiring that they specify who will have access to the data, how the data will be stored, how and at what point in the research personal information will be separated from other data, and whether the data will be retained at the conclusion of the study. They must provide a thorough description of interview instruments and questionnaires, and make sure that the informed consent of subjects will be obtained before interviews are conducted.

  Where identifiers are not required, they must not to be recorded. If identifiers are recorded, they should be separated from the data and stored securely. A linkage may be maintained only when necessary to conduct the research. Subjects must be given a clear explanation of how information about them will be handled. Information about the subject is not to be disclosed without the subject's consent. The protocol must clearly state who is entitled to see records with identifiers, both within and outside the project.

- **Randomized clinical trials**
  A primary ethical concern is one of fairness: If the trial therapy is known to be superior to currently available alternative therapies (i.e., prior research indicates that it is superior), it is unethical to assign subjects to the inferior treatment. It would not be ethical to perform a clinical trial comparing two treatments when there is a
third therapy that is known to be superior to either or both, unless there is some reason why that therapy is not useful for the study population.

Investigators must be able to state a null hypothesis (also called "theoretical equipoise": the assumption that subjects treated with therapy A - the trial therapy - will not differ in outcome from subjects treated with therapy B - the control therapy) before beginning a randomized clinical trial. A randomized controlled design may be justified where there is a current or likely dispute among expert members of the clinical community as to which of two or more therapies is superior in all relevant respects. The control treatment must be the best standard therapy currently available for the condition being treated.

- **Placebo**
  Placebos may be used in clinical trials where there is no known or available (i.e., FDA-approved) alternative therapy that can be tolerated by subjects.

A design involving a placebo control should not be used where there is a standard treatment that has been shown to be superior to placebo by convincing evidence. It has been argued that placebo controls must be used. The use of placebos in controlled clinical trials must be justified by a positive risk-benefit analysis, and subjects must be fully informed of the risks involved in assignment to the placebo group. A continued assignment of subjects to placebo may be unethical once there is good evidence to support the efficacy of the trial therapy. Clinical trials should be stopped or their protocols modified when there is sufficient evidence of either a beneficial therapeutic effect or unacceptable side effects.

Some drug trials involve a period during which all subjects receive only a placebo prior to the initiation of the study. This period is called a "placebo washout." The purposes of a washout period include: (1) terminating the effects of any drug the subject may have been taking before entering the clinical trial, so that the effects of the trial drug may be observed; (2) learning whether subjects cooperate with instructions to take drugs ("compliance"); and (3) learning which subjects are "placebo responders," in that they experience a high degree of placebo effect.

In some protocols, the investigators plan to exclude those subjects they find either poorly compliant or highly responsive to the placebo. The risks entailed in withdrawing subjects from therapy during a placebo washout period should be carefully evaluated; great care must be taken to exclude subjects who are vulnerable to injury if they are withdrawn from effective therapy. In studies involving a placebo washout, subjects should be told that at some point during the study all subjects will receive placebo treatment. Investigators, but not subjects, will know when subjects are receiving placebos for washout purposes, so that during the washout, the study is single-masked.

The IRB requires studies involving randomization and/or placebos to have a Data Safety Monitoring Board (DSMB) or a Data Safety Monitoring Plan (DSMP) to monitor adverse events.

The DSMB or DSMP is reviewed by the IRB on an annual basis or at more frequent intervals required by the IRB.

**PART VI – PRINCIPAL INVESTIGATOR RESPONSIBILITIES**

**General Responsibilities of Principal Investigators (PI):** The ultimate responsibility for the conduct of the study rests with the principal investigator (PI). He or she assumes overall administrative responsibilities for all aspects of the study, including the supervision of all co-investigators and research personnel to whom study responsibilities might be delegated.
While the PI may delegate responsibilities as appropriate, the PI is responsible for ensuring that all research activities are designed and performed in an ethical manner and in accordance with the IRB-approved protocol and application.

The PI must be qualified by education, training and experience in the area in which the research is being conducted. The PI must be familiar with the IRB-approved protocol, all applicable regulations and guidelines, state laws, and institutional policies pertaining to his or her human research protocol.

**Responsibilities for Protecting the Rights, Safety and Welfare of Research Participants:**

- Designing research studies that will most likely develop or contribute to generalizable knowledge, while minimizing risks and maximizing benefits.
- Ensuring adequate resources (i.e., personnel, time, facilities, funding, access to a study population) to conduct the research in a way that will protect the rights and welfare of participants and ensure the integrity of the research.
- Ensuring fair and equitable recruitment practices and avoiding recruitment practices that place participants at risk for coercion or undue influence.
- When a research consent form is required, obtaining the legally effective consent of the participant or the participant’s legally authorized representative prior to participation in research.
- Designing and carrying out the research with adequate data and safety monitoring, when appropriate.
- Responding promptly to participants' complaints and/or concerns or requests for information and reporting to the IRB any significant complaints and concerns regarding the conduct of human subjects research.
- Assuring that the protected health information (PHI) created or used in the research study, if any, is the minimum necessary to meet the research objectives, and that PHI is not reused or disclosed to any parties other than those described in the IRB-approved protocol.

**Responsibilities for Adhering to Regulatory, Institutional and IRB Requirements:**

- Conducting the research study as approved by the IRB.
- Contacting the IRB Office when uncertain about whether proposed activities require IRB review.
- Completing required Collaborative Institutional Training Initiative (CITI) online human research protection training.
- When applicable, completing any HIPAA research training.
- Ensuring that all human subjects research receives IRB review and approval prior to commencement, including screening and/or recruitment.
- Ensuring that the consent process meets the criteria for legally effective informed consent and documentation, as approved by the IRB.
- Providing a copy of the Patient Bill of Rights to each participant, unless waived by the IRB.
- Ensuring that the research study receives at least yearly continuing IRB review and approval.
- Providing disclosure of financial interests information and disclosing any other potential conflicts of interest that might affect the relationship with the research participant or the research outcome.
- Obtaining IRB review and approval before changes are made to approved protocols or consent forms according to IRB policy.
- Promptly notifying the IRB of serious adverse events and unanticipated problems according to IRB policies.
- Cooperating with any inquiries by the IRB concerning any research audits.
- Notifying the IRB if there is any change in his/her status as PI.
- Complying with FDA regulations and institutional policies when performing research involving FDA-regulated products.
Responsibilities for Training and Supervision of Study Personnel:

- Ensuring that all research personnel follow and adhere to the provisions of the IRB-approved protocol.
- Ensuring that only those individuals listed in the approved IRB application perform any research activity.
- Ensuring that all research personnel comply with IRB, institutional and federal policies pertaining to human subjects research.
- Ensuring that all research personnel are qualified experienced and appropriately trained for their roles and responsibilities.
- Ensuring that research personnel will be informed of any pertinent changes during the course of a study.
- Ensuring that research personnel will attend human subjects research education or additional training as needed.
- Ensuring that all research personnel completed the Collaborative Institutional Training Initiative (CITI) online human research protection training.
- Ensuring that all research personnel completed the HIPAA research training, if applicable.

Responsibilities for Research Record Keeping:

- Maintaining records of all approved IRB documents, correspondence and research protocol documents.
- Retaining all study records up to the completion of the study, plus seven years.
- For studies involving FDA-regulated products, retaining records in accordance with applicable FDA regulations.
- Making all research records accessible for review by authorized representatives of the IRB to ensure proper performance of the study and compliance with federal regulations and institutional policies.
- Maintaining confidentiality of research records in accordance with the IRB-approved protocol.

In accordance with federal regulations, the IRB must conduct continuing review of IRB-approved studies. The IRB developed an audit program for oversight of active research studies. This audit program is proactive and aimed at educating investigators about their ethical and regulatory responsibilities in conducting research.

Any instances of serious or continuing noncompliance with regulations or the requirements of the IRB must be reported to the appropriate institutional officials, Office of Human Research Protection (OHRP, and the FDA (if applicable) in accordance with 45 CFR 46.103 (b)(5) and/or 21 CFR 56.108(b).
References and Resources

PART I – HISTORY

Office for Human Research Protection
(http://www.hhs.gov/ohrp)

Office for Human Research Protection IRB Guidebook 1993
(http://www.hhs.gov/ohrp/archive/irb/irb_guidebook)

(http://www.hhs.gov/ohrp/archive/related)

Code of Federal Regulations DHHS Part 45 CFR 46 Protection of Human Subjects
Revised January 15, 2009   Effective July 14, 2009

National Institutes of Health Training Protection of Human Research Protection
(http://phrp.nihtraining.com)

PART II – VULNERABLE SUBJECTS

Code of Federal Regulations DHHS Part 45 CFR 46 Protection of Human Subjects
Revised January 15, 2009   Effective July 14, 2009
45 CFR 46 Subpart B
45 CFR 46 Subpart C
45 CFR 46 Subpart D

Office for Human Research Protection IRB Guidebook 1993
(http://www.hhs.gov/ohrp/archive/irb/irb_guidebook)

National Institutes of Health Training Protection of Human Research Protection
(http://phrp.nihtraining.com)

Baptist Health South Florida Institutional Review Board Policies and Procedures
BHSF 833.03 Vulnerable Subjects

PART III – SELECTION OF SUBJECTS

(http://www.hhs.gov/ohrp/archive/related)

Office for Human Research Protection IRB Guidebook 1993
(http://www.hhs.gov/ohrp/archive/irb/irb_guidebook)

National Institutes of Health Training Protection of Human Research Protection
(http://phrp.nihtraining.com)
PART IV – INFORMED CONSENT

Office for Human Research Protection
(http://www.hhs.gov/ohrp)

Office for Human Research Protection IRB Guidebook 1993
(http://www.hhs.gov/ohrp/archive/irb/irb_guidebook)

(http://www.hhs.gov/ohrp/archive/related)

Code of Federal Regulations DHHS Part 45 CFR 46 Protection of Human Subjects
Revised January 15, 2009   Effective July 14, 2009
45 CFR 46.116
45 CFR 46.117

Food and Drug Administration Clinical Trial Guidance Documents
(http://www.fda.gov/RegulatoryInformation/Guidances)

Food and Drug Administration DHHS Part 21 CFR 50 Protection of Human Subjects
Subpart B Informed Consent of Human Subjects

Baptist Health South Florida Institutional Review Board Policies and Procedures
BHSF 832.01 Advertisements and Recruiting Materials
BHSF 833.00 The Consent and Its Understanding
BHSF 833.01 General Requirements of Informed Consent

PART V – STUDY DESIGN

Office for Human Research Protection IRB Guidebook 1993
(http://www.hhs.gov/ohrp/archive/irb/irb_guidebook)

(http://www.hhs.gov/ohrp/archive/related)

Food and Drug Administration Clinical Trial Guidance Documents
(http://www.fda.gov/RegulatoryInformation/Guidances)

Baptist Health South Florida Institutional Review Board Policies and Procedures
BHSF 832.04 Medical Devices
BHSF 832.07 Investigational Drugs and Biologics
BHSF 832.08 Off-Label Use of Marketed Drugs, Biologics and Medical Devices
BHSF 832.09 Emergency Use of a Drug, Device or Biological Product
BHSF 832.10 Data Safety Monitoring

PART VI – PRINCIPAL INVESTIGATOR RESPONSIBILITIES

Food and Drug Administration Clinical Trial Guidance Documents
Food and Drug Administration Warning Letters
(https://www.fda.gov)

Office for Human Research Protection Compliance Oversight
(https://www.hhs.gov/ohrp)

Office for Human Research Protection Policy and Guidance for Investigators
(https://www.hhs.gov/ohrp)

Public Responsibility in Medicine and Research (PRIM&R)
Good Clinical Practice (GCP) – December 5, 2010

Baptist Health South Florida Institutional Review Board Policies and Procedures
BHSF 834.01 IRB Audit Program
BHSF 834.02 Notification of Noncompliance