

History of Human Subjects Protection

The history of human subjects protection begins with the *Nuremberg Code*, developed for the Nuremberg Military Tribunal, as standards by which to judge human experimentation conducted by the Nazis during World War II. The Code details many of what are now basic principles governing ethical conduct in research involving human subjects. The Code states:

“The voluntary consent of human subjects is absolutely essential.”

Freely given consent for participation in research is the foundation of ethical research involving human subjects. The Code also provides details implied by the requirement of freely given consent:

- ***capacity to consent***
- ***freedom from coercion***
- ***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 of the subject to withdraw at any time.

In the United States, regulations protecting human subjects were first promulgated by the Department of Health, Education and Welfare (now the Department of Health and Human Services). Those regulations provided regulatory status to the National Institutes of Health’s Policies for the Protection of Human Subjects, first issued in 1966. The regulations established the IRB as one mechanism through which human subjects would be protected. In July of 1974, the passage of the National Research Act established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. As part of its duties the Commission issued reports and recommendations identifying basic ethical principles that should underlie the conduct of research involving human subjects. The commission also recommended guidelines to ensure that research is conducted in accordance with those principles. The Commission’s report on these basic principles is called *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*.

In 1981, the Department of Health and Human Services revised their rules for dealing with research involving human subjects. These regulations, Federal Policy for the Protection of Human Subjects, are codified in Title 45 Part 46 of the Code of Federal Regulations. The Federal Policy is designed to make uniform the human subjects protection system in all relevant federal agencies and departments.

The institution encourages the conduct of research in and among its departments and in collaboration with other educational institutions and entities, while respecting the right of academic freedom in research, is also committed to adhering to basic ethical principles underlying the acceptable conduct of research involving human subjects as set forth in *The Belmont Report*. These basic principles: respect for persons, beneficence, and justice, are particularly relevant to the protection of human subjects in research, and are the accepted requirements for the ethical conduct of research.

- **Respect for Persons** involves recognition of personal self-worth and independence of individuals and requires special protection of people with diminished self-reliance for one reason or another.
- **Beneficence** is an obligation to protect persons from harm by maximizing beneficial results and minimizing possible risks.
- **Justice** requires that the distribution of benefits and risk of research be equitable.

The principle of respect for persons underlies the need to obtain informed consent; the principle of beneficence underlies the need to minimize risks; and the principle of justice requires that subjects be treated fairly. While it may be easy to define these principles, it is more difficult to apply them to research. It is the responsibility of the IRB to determine that these ethical principles are addressed in institutional research. Applying these ethical principles is explained below.

- **Respect for persons.** Required by the moral principle of respect for persons, *informed consent* contains three elements, information, comprehension and voluntary intent. First, subjects must be given sufficient information on how to decide whether or not to participate, including the research procedure(s); purposes, risks and anticipated benefits; alternative procedures; and a statement offering the subject the opportunity to ask questions and to withdraw at any time from the research. Second, subjects must be able to understand the information that is given to them. The presentation of information must be adapted to the subject's capacity to understand it. Finally, consent to participate must be given voluntarily. The conditions under which the agreement to participate is made must be free from coercion and undue influence. Further discussion of informed consent is made at other places in the manual.
- **Beneficence.** Closely related to the principle of beneficence, *risk/benefit assessments* "are concerned with the probabilities and magnitudes of possible harms and anticipated benefits." All possible harms, not just physical or psychological pain or injury, should be considered. This principle requires both protecting individuals against risk of harm and consideration of not only the benefits for the individual, but also the societal benefits that might be gained from the research. Risk benefit assessments are further discussed later in this manual.
- **Justice.** The principle of justice mandates that the *selection of research subjects* must be the result of fair selection procedures and must also result in fair selection outcomes. The justness of subject selection relates both to the subject as an individual and to the subject as a member of social, racial, sexual or ethnic groups. With respect to their status as individuals, subjects should not be selected either because they are favored by the researcher or because they are seen as outcasts by society. Social justice indicates that order of preference in the selection process (*e.g.* adults before children) and that some classes of potential subjects (*e.g.* the institutionalized, mentally infirm or prisoners) may be involved as research subjects only on certain conditions. Subjects should not be selected simply because they are readily available in settings where research is conducted. Selection of research subjects is further discussed later in this manual

The institution has standards for the conduct of research that mandate well-conceived and well-conducted research. The Institutional Review Board (IRB) has been established to assist in maintaining those standards. This manual provides a resource to new and existing members of the IRB to support efforts to maintain compliance with federal regulations governing the protection of human subjects. Although regulations and policies exist to guide ethical standards, they are no guarantee of ethical conduct in research. Individual researchers and IRB members have the responsibility to make ethical considerations in the conduct of research and to have a clear understanding of policies regarding human subjects. This manual is intended to provide a base for that understanding.

Functions and Operations

Responsibility and Authority

The IRB was formed in response to guidelines set forth by the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research. These principles, *The Belmont Report* and Title 45, Part 46 of the Code of Federal Regulations, guide research with human subjects and ensure their protection in the design and conduct of research. These federal regulations require that any institution requesting and receiving funds from a federal department or agency for research involving human subjects must assure that such research is reviewed and approved by the organization's Institutional Review Board. The institution has made the decision that all research with human subjects, whether funded or unfunded, or subject to the Federal regulation or not, will be reviewed and approved in accordance with the guidelines.

Any research that involves human subjects conducted by the institution's faculty, staff, residents or students, whether funded or unfunded, is under the jurisdiction of the IRB. Principal investigators who propose human subject research that is not specifically exempted must follow the guidelines for preparing and submitting proposals for review by the IRB. The IRB has the authority to suspend or terminate research that is not being conducted in accordance with the IRB's requirements, other institutional or federal requirements, or has been associated with any serious harm to subjects. Concerns regarding the conduct of research must be reported to the Chair of the IRB by any individual having such knowledge. Any suspension or termination of research must include a statement of the IRB's action and the Chair must report its decision promptly to the principal investigator, and the funding agency in the case of a sponsored project.

The IRB is responsible for determining that:

- *The welfare and rights of human subjects are adequately protected and informed consent procedures are in place, if necessary.*
- *Human subjects are not placed at unreasonable physical, mental, or emotional risk as a result of research.*
- *The benefits of the research outweigh the risks to subjects.*
- *The researcher(s) is/are qualified to conduct research involving human subjects.*

Meetings

Meetings of the IRB are convened by the Chair, or the Chair's designee, at a minimum of once per month. IRB Applications are due no later than one week prior to the meeting. If this deadline is not met, the application will not be reviewed until the next meeting. There will be no exceptions to this requirement. For regular meetings, members will receive meeting packets at least five days in advance. If there is no IRB business, the Chair, or designee, may cancel that meeting for the month and notify each member of that action, however, in the event that we do not have applications to review we may still have a monthly meeting in order to address training needs. Emergency meetings may be convened, as appropriate and require at least 24 hours notice. One third of the members of the IRB, one of whom must be a non-scientist must be present in order to constitute a quorum for the emergency meeting to be official.

Training

All new appointees to and continuing members of the IRB will receive training. As of July 1, 2002, all members of the IRB must complete the Computer Based Training for IRB Members from the National Institutes of Health. This course can be accessed at <http://ohsr.od.nih.gov>. The course takes approximately one hour to complete. A certificate of completion is generated at the end of the course as proof of taking the course. This certificate must be presented to the IRB and will be kept on file. The Chair, and others the Chair deems appropriate, will be responsible for ensuring that new appointees to the IRB receive training. Members must make a commitment to participate not only in the initial training, but also in ongoing training.

Changes in Policies and Procedures

Any policies and procedures governing the IRB may be changed at a regularly convened IRB meeting by a vote of the majority of the members present, based on a quorum of a majority of the total number of members on the IRB. Any changes made will be to facilitate the effective and efficient operation of the IRB and in no way will conflict with the rules promulgated as mandated federal statutes and regulations. Any changes in procedure and policy will be distributed to all members and potential investigators.

Membership

According to federal regulations, the IRB must have at least five members, with varying background to promote complete and adequate review of research activities conducted by SCHI personnel. Membership is comprised so that the IRB is sufficiently qualified through the experience, expertise and diversity of its members. This includes consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes to promote respect for its mission in safeguarding the rights and welfare of human subjects.

The IRB will include at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas. The IRB will also include at least one member who is not affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution. No member of the IRB may participate in the initial or ongoing review of a project in which the member has a conflict of interest except to provide information to the IRB. If the IRB reviews research that involves a vulnerable category of subjects (e.g. children, prisoners, pregnant women, handicapped or mentally disabled persons), the IRB may include one or more individuals with specific knowledge and experience working with these subjects, appointed temporarily for the project's review. These individuals are not allowed to vote with the IRB in these instances. A majority of the membership must be present at each meeting to make it valid.

Risk/Benefit Assessment

As stated earlier, risk/benefit assessments are concerned with the probabilities and magnitudes of possible harms and anticipated benefits. All possible harms, not just physical or psychological pain or injury, should be considered. This principle requires protecting individuals against risk of harm and consideration of not only the benefits for the individual, but also the societal benefits that might be gained from the research.

In determining whether the balance of risks and benefits results in a favorable ratio, the decision should be based on thorough assessment of information with respect to all aspects of the research and systematic consideration of alternatives. The Belmont Report recommends close communication between the IRB and the investigator and the IRB insistence on precise answers to direct questions. In weighing risk/benefit ratio the IRB should:

1. determine the validity of the presuppositions of research;
2. distinguish the nature, probability and magnitude of risk; and
3. determine whether the investigator's estimates of the probability of harm or benefits are reasonable, as judged by the known facts or other available studies.

Five basic principles or rules apply when making the risk/benefit assessment:

1. Brutal or inhumane treatment of subjects is never justified.
2. Risks should be minimized, including the use of human subjects.
3. IRBs must be meticulous in insisting upon sufficient justification for research involving significant risk to human subjects.
4. The appropriateness of involving vulnerable populations must be justified.
5. The proposed informed consent process must disclose relevant risks and benefits.

Selection of Research Subjects

The choice of the study design depends largely on the nature and goals of the research. Good methodology requires that studies be designed to minimize bias both in assignment to treatment groups (by randomizing) and in assessment of the outcome. Bias may enter into the study in several ways. The investigator may have strong beliefs or hopes regarding the success of a particular intervention or the truth of a particular hypothesis. These expectations may unconsciously influence the evaluation of the outcome of the research. To avoid this possibility, it is now accepted and preferred practice to conduct controlled investigations by dividing subjects (by randomization) into at least two groups: those who receive the experimental intervention (treatment group) and those who do not (control group).

Randomization is defined as assignment of different treatments, interventions, or conditions according to chance rather than systematically (e.g. as dictated by standard or usual response to conditions, 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 experimental intervention. It should be noted that any informed consent process for a research project must define the randomization process to subjects and clearly specify that the subject is just as likely as not to receive any experimental treatment.

Research Covered by and Exempt from Review

To comply with federal guidelines covering the protection of research subjects, and to ensure appropriate ethical management of research programs conducted by the institution's faculty, staff, residents and students, all funded and unfunded research proposals involving any risk to human subjects falls within the jurisdiction of the IRB.

Research that is covered by IRB review has potential risks to subjects including, but not limited to, the following:

- Research which involves the administration of drugs or other substances or subjects,
- Research involving pregnant women and/or fetuses in utero,
- Research involving subjects with life-threatening physical conditions,
- Research involving physically intrusive procedures,
- Research which previous experience (by the investigator or other investigators) has shown to create a potential of risk to subjects,
- Research which potentially could put the subject at risk for legal or civil liability or invade a subject's privacy in regard to sensitive aspects of his/her behavior (*e.g.*, illegal conduct, drug use, sexual behavior, alcohol use).

Research that is exempt from review is regarded as not having potential risk to subjects including the following:

- Research in which the risks of harm reasonably anticipated are not greater than those ordinarily encountered in daily life or during the performance of routine procedures in education and/or in the practice of psychology or medicine
- Research on the effectiveness of educational, classroom, and/or instructional strategies, provided that these strategies are familiar, and nonintrusive in their implementation
- Research using educational tests (cognitive, diagnostic, aptitude, and achievement) if subjects' identities are thoroughly protected.
- Research using survey procedures or interview procedures where subjects' identities are thoroughly protected and their answers do not subject them to criminal and civil liability
- Research involving the collection or study of existing data, documents, records, specimens, or other products, if these sources are publicly available or the information is recorded by the investigator in such a manner that *the subjects cannot be identified directly or indirectly.*

Criteria for Approval of Research

In order to approve proposed research at our institution, the IRB will determine that all of the following have been met, at a minimum:

- Risks to subjects are minimal
- Risks to subjects are reasonable in relation to anticipated benefits
- Selection of subjects is reasonable
- Informed consent will be sought from each prospective subject or the subjects legally authorized representative
- Informed consent will be appropriately documented
- When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects
- When appropriate, adequate provisions exist to protect the privacy of subjects and to maintain the confidentiality of data
- Additional safeguards have been included in the study to protect the rights and welfare of vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons or economically or educationally disadvantaged individuals, as necessary.

Types of Review

Full Review

A full review of proposed research shall take place at convened meetings of the IRB at which one half of the members of the IRB, one of whom must be a non-scientist, must be present. In order to approve a protocol, the IRB must determine that the criteria for approval have been met. In order for a protocol to be approved, it must receive approval of a majority of the members present at the meeting.

Expedited Review

Expedited review allows the IRB to use an abbreviated review procedure for research protocol involving human subjects. To qualify for an expedited review, two criteria must be met:

1. The research must involve no more than minimal risk to the human subjects, **and**
2. The research must consist entirely of one or more of the following specific activities:
 - Collection of hair and nail clippings, deciduous teeth and permanent teeth in the event of an extraction
 - Collection of excreta and external secretions including sweat, uncannulated saliva, placenta removed at delivery and amniotic fluid at the time of rupture of the membrane prior to or during labor
 - Recording of data from subjects 18 years of age and older using noninvasive techniques routinely employed in clinical practice. This does not include x-rays, microwaves or any electromagnetic radiation outside the visible range.
 - Collection of blood samples by venipuncture, in amounts not exceeding 450 milliliters in an eight week period and no more often than twice per week, from subjects who are 18 years of age or older and who are in good health and not pregnant.
 - Collection of both supra- and sub gingival dental plaque provided it is in a routine prophylactic setting.
 - Voice recording made for research purposes, such as investigations of speech defects.
 - Moderate exercise for healthy volunteers.
 - The study of existing data, documents, records, pathological specimens or diagnostic specimens.
 - Research on individual or group behavior characteristics of individuals, such as studies of perception, cognition, game theory or test development.
 - Research on drugs or devices where an investigational device exemption is not required.

In addition, expedited review may be used where there are minor changes in previously applied research during the period for which approval is authorized.

Expedited review may be carried out by the IRB Chair or by one or more reviewers designated by the Chair from among the members of the IRB. When conducting an expedited review, IRB members may exercise all of the authorities of the IRB, except that reviewers may not disapprove the research. The options are to approve the protocol or defer it for a full review. A research activity may be disapproved only after a full IRB review has been conducted. All IRB members must be advised of research proposals that have been approved at the next regularly scheduled meeting.

Continuation/Renewal

Continuing review of research must be conducted at intervals appropriate to the degree of risk, but not less than once per year. The IRB cannot approve a research project for more than 12 months. Review for continuation may be conducted by expedited review if no changes have been made to the research protocol and no adverse or unexpected reactions or side effects have occurred or are expected. However, the full IRB will be given the opportunity to review the renewal/continuation report. In all other instances, continuing review will be conducted by the full IRB.

Revision

If the investigator, during the course of conducting the research, revises the research protocol (e.g., makes changes to the informed consent, survey instruments, number or nature of research subjects, etc.), the principle investigator will notify the IRB Chair immediately. The Chair will determine the need for additional review, a full or expedited review as necessary, and notify the IRB members.

Types of IRB Actions

The IRB shall review and have the authority to approve, tentatively approve pending receipt of additional information, or disapprove the subject research according to the following:

Approval

The protocol is approved as submitted.

Pending Approval

A protocol is considered pending when the problems identified in the protocol are not serious and generally fall into two categories: 1) the investigator needs to clarify an aspect of the study or provide additional information, or 2) minor changes need to be made in the consent document. In these cases, approval can be given after the investigator rewrites the informed consent and/or submits to the Chair a written response to the IRB's questions and concerns. The Chair will then poll IRB members to receive final approval.

Disapprove

The IRB will disapprove the proposed research if it places the subjects at risks that far outweigh the benefit or value of the knowledge to be gained, or it raises serious ethical questions. A research activity can be disapproved only after a full IRB review has been conducted.

In each of the above cases, the IRB will notify the principal investigator of the results of its action in writing.

Informed Consent

One significant outcome of the Nuremberg medical trials was the establishment of the Nuremberg Code of 1947, which set forth ten principles for conducting research involving human subjects. The first principle states, “The voluntary consent of human subjects is absolutely essential.” No investigator may involve a human being as a subject in research unless the investigator has obtained the subject’s informed consent. It should be noted that informed consent is a *process*, not a form that must be completed. The process of obtaining informed consent at SCHI must contain the following elements:

1. It should be obtained from the subject or the subjects legally authorized representative.
2. It should be in language understandable to the subject or his legal representative.
3. It should be obtained under circumstances that provide the subject with the opportunity to consider whether or not to participate, and that minimizes the chance of coercion or undue influence.

When reviewing informed consent processes in research protocols, researchers and IRB members should review the following checklist of items.

Informed Consent Checklist – Basic and Additional Items

Basic Elements

- A statement that the study involves research.
- An explanation of the purposes of the research.
- The expected duration of the research.
- A description of the procedures to be followed.
- Identification of any of the procedures which are experimental.
- A description of any reasonably foreseeable risks or discomforts to the subject.
- A description of benefits to the subject/society that may be reasonably expected from the research.
- A disclosure of appropriate alternative procedures or courses of treatment that may be beneficial.
- A statement describing the extent to which confidentiality of records will be maintained.
- For research involving more than minimal risk, an explanation as to whether any compensation or medical treatments are available, what the compensation consists of and where further information may be obtained.
- An explanation of whom to contact about questions regarding:
 - The research project
 - The subject’s rights
 - Injury during participation in the project.
- A statement that participation is voluntary, refusal to participate involves no penalty or loss of benefits, and the subject may discontinue participation in the research without penalty or loss of benefits.

Additional Elements (as necessary)

- ❑ A statement that the treatment or procedure may involve risks to the subject (or embryo or fetus), which are currently unforeseeable.
- ❑ Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.
- ❑ Additional costs to the subject that may result from participation in the research.
- ❑ The consequences of the subject's decision to withdraw from the research and procedures for termination of participation by the subject.
- ❑ 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 as they occur.
- ❑ The approximate number of subjects involved in the study.

Tips for Reviewing Consent Procedures.

- ◆ Informed consent is process. Information must be presented to enable persons to voluntarily decide whether or not to participate as a research subject. The procedures used in obtaining informed consent should be designed to educate the subject population in terms they can understand. Therefore, informed consent language and its documentation must be written in "lay language." Use of scientific jargon and legalese is not appropriate. Think of the document primarily as a teaching tool not a legal instrument.
- ◆ Describe the overall experience that will be encountered. Explain the research activity and how it is experimental. Inform the human subjects of the reasonably foreseeable harms, discomforts, inconveniences and risks that are associated with the research.
- ◆ Describe the benefits that subjects may reasonably expect to encounter. There may be none other than a sense of helping the public at large. If payment is given to defray the incurred expense for participation, it must not be coercive in amount or method of distribution.
- ◆ Describe any alternatives to participating in the research project. For example, in drug studies the medication(s) may be available through their family doctor or clinic without the need to volunteer for the research project.
- ◆ Federal regulations insist that the subjects be told about the extent to which their personally identifiable information will be held in confidence. For example, some studies require disclosure of information to other parties. The IRB will determine the level of adequate requirements for confidentiality in light of its mandate to ensure minimization of risk and determination that the residual risks warrant involvement of subjects.
- ◆ If research related injury is possible in research that is more than minimal risk an explanation must be given of whatever voluntary compensation and treatment will be provided. It should be noted here that injury does not only refer to physical injury but also to psychological, social, financial or other injuries.
- ◆ Federal regulations prohibit waiving or appearing to waive any legal rights of subjects. In no way should subjects ever be given the impression that they have agreed to and are without recourse to seek satisfaction beyond what the institution has voluntarily chosen to do in response to research injury.

- ◆ Federal regulations provide for the identification of persons who are knowledgeable about subjects of the research, rights as a research subject and research-related injuries. These people must be explicitly stated. Additionally, a single person is not likely to be appropriate to answer questions related to all three subjects. Therefore, the investigator is usually named as the person to answer questions about the research. Questions about rights as a subject and research-related injury are best answered by a member of the IRB, an ethics committee or other informed administrative official). At our affiliated institutions, the chair of the IRB will normally be designated as this person. Therefore, each consent document should have at least two names to contact with various questions.
- ◆ Federal regulations are also very clear that any consent language must explicitly state that participation by a subject is completely voluntary and that any subject has the right to withdraw from a research project at any time.
- ◆ Additional requirements may be imposed by the IRB that are not specifically listed in Federal regulations but that are protective of institutional policy and local law. However, these requirements may not be less stringent than the Federal regulations.

Waiver of Consent

There are two circumstances in the regulations that give IRBs authority to waive the required consent. The first waiver authority is applicable to research or demonstration projects conducted by or subject to the approval of state or local government officials and are designed to study, evaluate, or otherwise examine:

- Public benefit of service programs,
- Procedures for obtaining benefits or services under those programs
- Possible changes in or alternatives to those programs or procedures
- Possible changes in methods or levels of payment for benefits or services under those programs

and,

- The research could not practicably be carried out without the waiver or alteration.

The second waiver authority is for consent procedures that do not include, or which alter some or all of the elements of informed consent set, or waive the requirements to obtain informed consent provided the IRB finds and documents that:

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

Documentation of Informed Consent

Federal regulations also require that the informed consent process be documented. Informed consent at SCHI will be documented by using a written consent form approved by the IRB. The subject or the subject's authorized representative will sign the form. A copy must be given to the person signing the form.

Two types of consent are permissible including:

1. A written consent document that includes all of the basic elements as described above.
2. A short form which states that the elements of informed consent have been obtained from the subject orally or in some other manner acceptable to the IRB. At the minimum, the short form must meet the following conditions:
 - A written summary of what will be said to the subject must meet IRB approval
 - A witness must be present at the time of oral presentation to the subject
 - The subject or his or her representative signs the form
 - The witness signs the short form and the written summary, and
 - A copy of both the signed short form and the written summary is given to the person signing the form (either the subject or his/her representative).

The IRB may waive the requirement to obtain a signed consent for the some or all of the subjects in the following instances:

- The only record linking the subject and the research would be a consent document and the principal risk would be harm resulting from breach of confidentiality, or
- The research presents no more than minimal risk and involves no procedures for which consent is normally required.

However, the IRB may still require that the investigator provide subjects with a written statement regarding the research.

An example of a consent form with all of the basic elements is included in this manual on pages 18 – 23.

Sample Consent Form

TITLE OF PROJECT

INVESTIGATOR: Name
Address
City, State Zip
Phone

➤ **Why have I been asked to take part in this research study, and who is conducting it?**
You are being asked to take part in this study because your breast cancer has spread to one or more organs in your body. This study is being conducted by (*Name of Investigator and Institution*). Patients in clinical trials include only those who choose to take part. Please take your time to make your decision. We encourage you to discuss your decision with your doctor, family and friends.

Statement of the Purposes of Research

➤ **Why is this research study being done?**
The reason for doing this study is to evaluate the effects, good and bad, of a combination of two commonly used chemotherapy (cancer fighting) drugs. We want to see if the amount of dendritic cells (cells that may increase cancer immunity), in the blood affects how well the chemotherapy works, and how well the bone marrow stimulant may increase these cells. We will also learn more about any side effects you experience.

of participants in study

➤ **How many people will take part in the study?**
About 20 women will take part in the study.

This section describes the procedures

➤ **What is involved in the study?**
Before you begin the study. First we will need to find out whether you are able to be on the study. You will be asked to give information about your medical history and undergo the exams and tests listed below. If you have had any of them recently, your doctor may decide not to repeat them. The exams and tests include:

- Physical exam
- Chest x-ray
- EKG
- Blood tests
- Bone scan
- MUGA scan or echocardiogram (tests to see how well your heart works)
- Possible CT scans of areas with metastatic cancer

These exams and tests are not experimental; they are routine. They are standard good medical care even if you do not join the study. If you do join, some of these procedures may be done more often than if you were not taking part in the study. They may be done on an outpatient basis at your doctor's office or clinic, or in the hospital.

During the study. If you are eligible for and agree to take part in the study, you will be registered into the study.

We will need to do blood tests to see if the amount of drug you are receiving during your chemotherapy should be changed or delayed. The test will help monitor any side effects you may have and measure the number of dendritic cells in your blood. After your treatment is done your doctor will ask you to come in for follow-up blood tests in two months and as needed depending on your clinical condition.

Group assignment and treatment. You will be registered into the study mentioned above if the number of dendritic cells in your blood is high or low after four days of receiving GM-CSF (a medication that stimulates the bone marrow) one week before starting chemotherapy.

Treatment Schedule:

One week before chemotherapy, GM-CSF will be given daily Monday through Thursday then you will have blood tests to determine the amount of dendritic cells that are in your blood.

After receiving blood results you will be put on the following schedule.

Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Mitoxantrone	GM-CSF	GM-CSF	GM-CSF	GM-CSF	No treatment	No treatment
Taxol						

This schedule will repeat weekly for 8 weeks total.

So that you do not develop an infection, you may also be given an *antibiotic*, either ciprofloxacin hydrochloride (also known as Cipro) or trimethoprim/sulfamethoxazole (known as Bactrim DS), between your chemotherapy treatments. Tell your doctor or nurse if you are taking any drugs other than those you receive in this study. They need to make sure that these drugs will not cause problems with your study treatment.

➤ **How long will I be in the study?**

Your chemotherapy treatment will last for 2 months but may be continued longer if your cancer is responding.

We would like to keep track of your medical condition for the rest of your life to look at the long-term effects of the study. However, your doctor may take you off the study drugs if one of the following happens:

- The study treatment does not work for your cancer,
- You develop a serious side effect that you cannot tolerate or that cannot be tolerated with other medications,
- Your health gets worse,
- You are unable to meet the requirements of the study (for example, you cannot take the medicine as prescribed or cannot return for follow up visits)
- New information about the study drugs or other treatments for breast cancer becomes available.

This section details how long the participant will be in the study and circumstances under which participation may be terminated by the investigator.

In addition, your participation in this study may be ended because (*List appropriate Investigator, Institutions or IRB*) find it necessary to limit or stop the study.

➤ **What are the risks of the study?**

There are risks involved in taking the drugs in this study, and there may be side effects. Most of these are listed below, but they will vary from person to person. Talk with your study doctor about this. If you want to read more about these study drugs, please ask your doctor or pharmacist for more information.

Risks of participating in the study are detailed here

Side effects that are likely to occur from the chemotherapy:

- Nausea
- Vomiting
- Diarrhea
- Fluid retention
- Fever
- Allergic reaction (itching, hives, flushing, hypersensitivity, shortness of breath, wheezing, chest tightness, skin rashes, fever, chills, muscle stiffening, severe breathing problems)
- Weakness/loss of strength
- Fatigue
- Pain in muscles or joints
- Loss of appetite
- Complete hair loss
- Skin and nail discoloration
- Nail changes
- Sores in mouth and/or throat
- Prickling/tingling of skin
- Lowered white blood cell count (may lead to infection)
- Lowered red blood cell count (may lead to anemia, tiredness, shortness of breath)
- Infection
- Irregular or permanent stoppage of menstrual cycle
- Inability to get pregnant
- Time away from work

In addition, it is **possible** but unlikely you may experience one or more of the following during your chemotherapy: ulcers in the stomach or bowels; darkening of the soles of the feet or palms of the hands; skin damage (due to leakage of drug); scaling of the skin; reddening of the skin; changes in blood test results that indicate possible liver injury; damage to kidneys; pain (in the back, stomach or head); lowered platelets (leads to increases in bruising or bleeding); blood in urine; low sodium; high or low blood pressure; hardening of the walls of the veins; uric acid in the blood; irregular heart beat; chest pain; heart failure; drowsiness; lung damage; eye problems; inflammation of veins. In **rare** circumstance, you may experience liver failure, seizures, acute leukemia or heart damage.

You will need to take a daily shot of a bone marrow and blood-cell stimulating drug, GM-CSF to help prevent infection due to low white blood cell counts. GM-CSF helps your white blood cells multiply to fight any possible infections and may also stimulate the numbers of cancer fighting dendritic cells. Patients receiving GM-CSF have experienced fever, chills, nausea, vomiting, diarrhea, fatigue, weakness, headache, decreased appetite, blood clots, and rapid or irregular heartbeat or other heart problems. You may experience a feeling of faintness; facial flushing; pain in the bones, muscles, chest, abdomen or joints; local reaction at the site of injection; flashes; and kidney or liver dysfunction. Eosinophilia or other blood component abnormalities may occur.

There have been infrequent reports of fluid accumulation or worsening of pre-existing fluid accumulation in the extremities, in the lungs or around the heart which may result in breathing problems or heart failure. Rarely, patients have developed acute allergic reactions. There have also been reports of low blood pressure, hypoxia, transient loss of consciousness, and difficulty in breathing after the first injection of GM-CSF. These signs may or may not recur with additional injections of GM-CSF. There may be other side effects that could occur.

You are at risk for any of the side effects discussed for as long as you are receiving treatment as part of this study. There may be other side effects that we cannot predict. You should discuss risks and side effects with your oncologist.

Risks associated with pregnancy are highlighted

Risks related to pregnancy: You should **not** become pregnant while on this study because the drugs can affect an unborn baby. As about counseling and more information about preventing pregnancy if this applies to you. Also, you should not nurse your baby while on this study. Some of the drugs used in the study may make you unable to have children in the future. If you think that you could be pregnant, please notify your physician immediately. Anyone who is sexually active and of child bearing potential must use an effective method of birth control while on the study.

Statement about benefits

➤ **Are there benefits to taking part in this study?**

There may or may not be direct medical benefit to you from taking part in this study. All of the drugs used in this study have been given successfully to women with breast cancer, but we cannot always predict who will respond well to this treatment. We hope the information learned from this study will help future patients with breast cancer.

➤ **What other treatment options are there?**

Instead of being in this study you can decide to have:

- Chemotherapy with these or other drugs known to be effective for treating breast cancer,
- No treatment

Disclosure of Alternative Procedures

These options are available to you at this center or other centers, even if you do not take part in this study. Please talk with your doctor about these and other options before you enter the study and about other options that may become available during the trial.

➤ **How will information about me be kept private?**

Confidentiality

We will try to keep personal information about you as private as we can. We cannot guarantee absolute privacy. Your personal information may be disclosed if required by law. Organizations that may inspect and/or copy research records for quality assurance and data analysis include the groups listed below. Your research records will include things such as your medical history, results of your blood tests and exams, reports from your surgery and treatment, reports of your office visits, and your mammogram films and reports.

- The Food and Drug Administration (FDA)
- Immunex, which is supplying the study drug GM-CSF free of charge through MSU

The following section describes additional costs that the study subject may incur.

➤ **What are the costs?**

Taking part in this study may lead to additional costs for you or your insurance company due to the extra blood tests required. The blood tests for dendritic cells will be paid for by Immunex through MSU. Please ask about any expected added costs or health insurance problems. If you are injured or become ill from taking part in this study, emergency medical treatment is available but will be provided at usual charge. No funds have been set aside to pay you in the event of an injury. You or your insurance company will be charged for continuing medical care and/or hospitalization.

You will not be paid for taking part in this study. During the study, if GM-CSF is no longer provided free, you may have to pay for the amount of drug needed to complete the study. However, we do not expect this will happen.

You understand that your participation in this research will necessitate additional procedures, which will be discussed with you. The costs for these are usually covered by your insurance. You understand those costs not covered by insurance will be provided by research funds. However, you will still remain responsible for the insurance deductible.

➤ **Do I have to be part of the study?**

You may choose to either take part, or not take part in this research study. If you have questions about the study, you will have a chance to talk with one of the study staff. Do not sign this form unless you have had the chance to ask questions and have received satisfactory answers. You may also wish to discuss this matter with a relative, friend or your regular doctor.

Statement that participation is voluntary, subject can withdraw, procedures for withdrawing and no penalty for doing so.

➤ **What are my rights as a study participant?**

Even after you agree to take part in this study, you may withdraw at any time. Before withdrawing, you should notify one of the people involved with this research. This will allow that person or someone else supervising the research to inform you of any medical risks associated with withdrawing. You can choose to withdraw one of two ways. In the first, you can stop your study treatment, but still allow the study doctor to follow your care. In the second, you can stop your study treatment and not have any further contact with study staff. Either way, there will be no penalty to you.

Your decision will not affect your routine medical treatment, your relationship with those treating you, or your relationship with this institution. If you withdraw from the study therapy, you will still be offered all available care that suits your needs and medical condition. You understand that your participation is voluntary and you may refuse to participate without penalty or loss of benefits.

Significant new findings developed during the research may relate to your willingness to continue participation will be provided to you.

➤ **Where can I get more information about cancer and its treatment?**

You can call the Cancer Information Service at 1-800-4-CANCER or visit the National Cancer Institute’s Clinical Trials Web Site at <http://cancertrials.nci.nih.gov>.

If you would like additional information about the drugs used in this trial and their side effects, you should ask your doctor or pharmacist, or visit the Medscape web site at <http://www.medscape.com>.

You can also get information at any time from the doctor in charge of your medical care in this study.

➤ **Who can I call if I have questions or problems?**

For questions about the study or research-related injury call (*Investigator or IRB Member or other appropriate person*) at the number listed in the next paragraph. For questions about your rights as a research participant, call the contacts listed in the next paragraph. The Institutional Review Board (IRB) is a group of people who review research studies to protect your rights.

COMPENSATION FOR ILLNESS OR INJURY: You understand that in the event of a physical injury or physical illness resulting from your participation in this research study, no funds are available for compensation but that your immediate emergency medical treatment which may be necessary will be made available to you for which payment shall be your responsibility. In the case of injury related to this research study you should contact (*the local investigator or IRB member – list addresses and daytime and night time phone numbers*).

VOLUNTARY CONSENT: You certify that you have read this consent form or that it has been read to you and that you understand its contents. Any questions you have pertaining to the research study have or will be answered by (*List Investigator and contact information*). Any questions you have about your rights as a research subject will be answered by (*Usually List an IRB member or other institutional official*).

A copy of this consent will be given to me.

My signature below indicates that I have been informed of the study information, that any questions I had have been fully answered, and that I have freely agreed to continue to participate in this study.

A statement about who to contact with questions about rights as a research subject, injuries or the research project, and any compensation that is available to subjects.

Date

Patient’s Signature

Date

Witness’ Signature

AUTHORIZATION TO USE AND DISCLOSE PROTECTED HEALTH INFORMATION

HIPAA Authorization for Use with Informed Consent

This study requires the use and release of your current and/or future health information. This form tells you your rights about your health information in the study. This form also lists who you will agree to let use, release, and get your health information.

You are free to not allow these uses and releases by not signing this form. But if you do that, you cannot participate in the study.

These are the types of your health information that may be used or shared in this study:

- Your name, gender, initials, address, telephone number, and date of birth, and social security number
- All of your medical and research records
- Insurance information

By signing this form, you allow the use, sharing, and copying of your health information to carry out the study by:

- Your healthcare providers (like doctors and hospitals) which are not part of the study
- Your health plans or your employer
- The Study Doctor
- Other healthcare providers such as labs which are part of the study.

These people will use, share, copy or release your health information to carry out the study. This includes treatment that is part of the research.

You also allow the Study Doctor and other healthcare providers who are part of the study to release your health information to:

- The Sponsor, its corporate affiliates, and any contractors or partners it may have
- Research sites for this study, including this hospital, and including each site's research staff and medical staff
- Research monitors and auditors
- Oversight bodies like Institutional Review Boards (IRBs), Ethics Committees, and Data Safety Monitoring Boards
- Government agencies such as the Food and Drug Administration in the U.S. and other countries

Usually you can see your health information. But you agree that you will be allowed to see your health information for this study until it ends.

This permission has no expiration date, so it does not end unless you cancel it, even if you leave the study. You can cancel this permission any time by writing to the Study Doctor. However, your cancellation will not apply to health information already obtained by health care providers and health plans where they have:

- Already used or released your health information
- Acted in reliance on your permission

If you cancel your permission, you will be withdrawn from the study.

Not signing this form or later canceling your permission will not affect your.

- Health care treatment outside the study
- Payment for health care from a health plan
- Ability to get health plan benefits

Federal law may allow someone who gets your health information from this study to use or lease it in some way not discussed in this form. You will be provided a copy of this form.

I have read this form. I understand it and agree to its terms.

Signature of Participant

Name of Participant

Date

The contact information of the subject or personal representative who signed this form should be filled in below:

Address:

Telephone:

_____ (daytime)

_____ (evening)

E-Mail Address (optional): _____

(A copy of this signed form must be given to the Participant.)

Elements of Research Design

The value of any research project depends upon the integrity of the results. One of the ethical justifications for research involving human subjects is the social value of advancing scientific understanding and promoting human welfare by improving health care. But if the research study is so methodologically flawed that little or no reliable information will result, it is unethical to put subjects at risk or even to inconvenience them through participation in such study. IRBs struggle with answering questions about their responsibility to review the underlying science of the proposed research. If it is not good science it is not ethical. Federal regulations under which IRBs operate do not clearly call for IRBs to review the scientific merit of research. However, they do require that IRBs determine whether, “risks to subjects are reasonable in relation to...the importance of knowledge that may reasonably be expected to result.” If the underlying science is no good, then surely no important knowledge may reasonably be expected to result.

Without clear direction on this point, the institution’s IRB will take the following approach: where an investigator conducting the research under review is seeking funding from the federal government or other funding agency, review of the science will be left to the agency’s peer review process. The IRB provides a less detailed examination to satisfy itself that there are no obvious flaws that would place subjects at unnecessary risk. Where the protocol will not receive such a detailed scientific review, the IRB will review the research design more carefully. The IRB will provide a critical analysis of the scientific merits of the research protocol and require that investigators correct design flaws before receiving final IRB approval, but the IRB must recognize its limits in this regard as well. The IRB is not a body that should take on the task of redesigning protocol, but should take steps to ensure that the proposed scientific process is sound to ensure valid results. Although IRB members do not need to be experts in scientific or statistical methodology, they should understand the basic features of experimental design.

The pursuit of science is an attempt to understand the physical world. Basic to scientific inquiry is the acceptance of the philosophical perspectives known as empiricism and determinism. Scientists take for granted that knowledge results from experience and is based on observations of physical events. Moreover, these physical events are assumed to follow physical laws in that they depend on causal factors that can be discovered.

Scientific understanding, then, must be based on objective, systematic observation of physical events and on analytical reasoning, or inference that is logical. The words objective and systematic refer to critical characteristics of the observations upon which science is based. Objective observations can be experienced directly and are repeatable, making it possible for scientists to verify others’ work. Systematic observations are obtained under clearly specified, controlled conditions that can be measured and evaluated. Research methodology provides the tools needed to produce objective and systematic observations, called empirical data, and to ensure that conclusions based on observations are logical.

Scientists develop theories to organize their empirical observations. A theory is a set of principles that attempts to explain the causal factors underlying the related scientific observations. The usefulness of any theory depends on its internal consistency, its ability to account for existing data, and its precision in prediction. Scientists use hypotheses to generate predictions that can be tested empirically. It is important to understand that scientific theories and hypotheses can never be proven true but can only be supported or not supported by currently available data.

Biomedical investigations can be broadly categorized into two types: experimental studies and descriptive studies. A true experimental study is one in which subjects are *randomly assigned* to groups that experience carefully controlled treatments and are manipulated by the experimenter according to strict logic allowing causal inference about the effects of the treatments that are under investigation.

Descriptive studies, although objective and systematic, lack the rigid control achieved through random assignment of subjects and precise manipulation of treatment conditions. As a result, causal inferences cannot logically be derived from descriptive studies. Types of descriptive studies are quasi-experimental (an experimental study where subjects are not randomized), correlational studies, record reviews, case histories, and observational studies.

TABLE OF CONTENTS

SECTION	PAGE
History of Human Subjects Protection	1
Functions and Operations	4
Responsibility and Authority.....	4
Meetings	4
Training	5
Changes in Policies and Procedures	5
Membership	6
Risk/Benefit Assessment	7
Selection of Research Subjects	8
Research Covered by and Exempt from Review	9
Criteria for Approval of Research.....	10
Types of Review	11
Full Review.....	11
Expedited Review.....	11
Continuation/Renewal	12
Revision.....	12
Types of IRB Actions	13
Approval.....	13
Pending Approval.....	13
Disapprove.....	13
Informed Consent.....	14
Informed Consent Checklist – Basic and Additional Items	14
Basic Elements	14
Additional Elements (as necessary)	15
Tips for Reviewing Consent Procedures.	15
Waiver of Consent.....	16
Documentation of Informed Consent	17
Sample Consent Form	18
Authorization to use and disclose protected health information	24
Elements of Research Design	26

**ACORN- AFFILIATED CHM-OB/GYN RESIDENCY NETWORK
INSTITUTIONAL REVIEW BOARD**

**MEMBER HANDBOOK
SEPTEMBER 2007**