

MARQUETTE GENERAL HEALTH SYSTEM
Regional Medical Center

CONSENT TO PARTICIPATE IN AN INVESTIGATIONAL STUDY

TITLE: S0307, "Phase III Trial of Bisphosphonates as Adjuvant Therapy for Primary Breast Cancer"

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This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this study because you have Stage I, II, or III breast cancer that is currently in remission.

Why is this study being done?

This study is investigational and is being done to find out if adding a drug (a bisphosphonate) to hormonal therapy or chemotherapy will help prevent cancer from spreading to the bones or other parts of the body. "Bisphosphonates" are a group of drugs that have strong effects on the bones and have been shown to strengthen the bones in many patients who take them.

How many people will take part in the study?

About 6,000 people will take part in this study.

What will happen if I take part in this research study?

Before you begin the study ...

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- Medical History and Physical Exam
- Weight and Performance Status

- Disease Assessment
- Routine laboratory tests: including a serum creatinine blood test (to measure kidney function) will be performed within 7 days prior to starting study
- CT and bone scans (as needed for disease assessment): a series of detailed pictures of areas inside the body from different angles; the pictures are created by a computer linked to an x-ray machine
- Dental examination: to be performed within 6 months prior to registration.
- Women of child-bearing potential must have a pregnancy test performed within 72 hours prior to initiation of treatment.

During the study ...

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures. They are part of regular cancer care.

- Medical History and Physical Exam
- Weight and Performance Status
- Disease Assessment
- Routine laboratory tests (to measure your liver and kidney function): You will need to have your kidney function tested every month for the first 6 months, and then once every 3 months while on treatment.
- CT and bone scans (as needed for disease assessment); and at the end of treatment: series of detailed pictures of areas inside the body from different angles; the pictures are created by a computer linked to an x-ray machine
- Dental examination (at the end of treatment): It is important to undergo routine dental exam and care while on the study. Be sure to discuss with your study doctor before having dental procedures while on chemotherapy.

You will need these tests and procedures that are either being tested in this study or being done to see how the study is affecting your body. A sample of your tumor tissue and your blood will be requested for current and further scientific studies. At the end of this form you can indicate your preferences related to the use of these samples.

- Tumor block for PTHrP testing and banking: a sample of your tumor from the original biopsy will be removed and analyzed for parathyroid hormone related protein (PTHrP) to see if this predicts the risk of your breast cancer spreading to the bones. If you consent, any remaining sample will be stored frozen for future scientific studies.
- Serum for N-telopeptide testing and banking: an additional blood sample (approximately 10 mL or 2-3 teaspoons) will be collected at pre-study and analyzed for the substance n-telopeptide to see if high levels will predict if breast cancer will spread to the bones. If you consent, any remaining sample will be stored frozen for future scientific studies.

You will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. Neither you nor your doctor can choose the group you will be in. You will have a one-in-three chance of being placed in any group.

If you are in Group 1 (often called "Arm 1") you will be given 4 mg (or less based on how your kidneys are working) of **zoledronic acid** through a needle in your vein every month for the first six months and then once every three months after that for thirty months.

If you are in Group 2 (often called "Arm 2") you will take 1,600 mg of **clodronate** by mouth once a day, every day for thirty-six months.

If you are in Group 3 (often called "Arm 3") you will take 50 mg of **ibandronate** by mouth once a day, every day for thirty-six months.

If you are assigned to either Group 2 or 3, it is strongly encouraged that you record the number of pills you take each day on a calendar. During visits with your study doctor (at Months 6, 12, 24, and 36) you will be asked how many pills were missed during the last month of protocol treatment. This will be done in order to determine if you are having any problems taking the drug and to confirm you are taking it as directed.

Study Chart

The chart below shows what will happen to you during this study, as explained previously. The left-hand column shows the weeks in the study, and the right-hand column tells you what to do during that week.

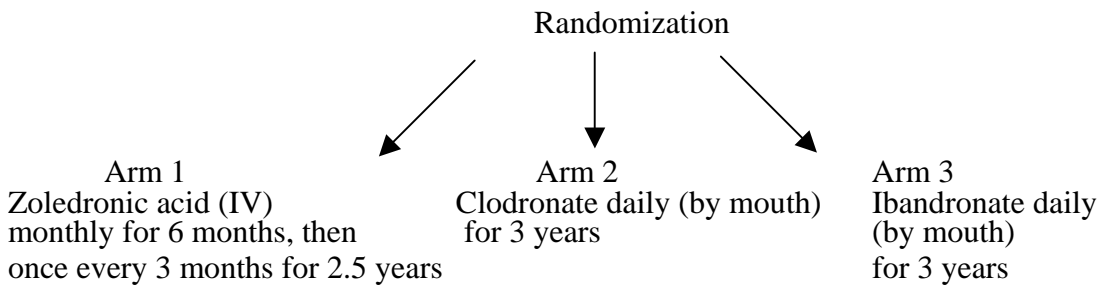
Day	What you do
Within 6 months before starting study	<ul style="list-style-type: none"> • Get routine dental examination.
Within 28 days before starting study	<ul style="list-style-type: none"> • Get routine blood tests. • Get chest x-ray; chest CT and bone scans (as needed for disease assessment). • Get medical history, physical examination, and performance status. • Tissue from the original tumor biopsy will be submitted for research studies (if consent is established).
Within 7 days prior to starting study	<ul style="list-style-type: none"> • Get kidney function test.
Within 72 hours prior to starting study	<ul style="list-style-type: none"> • If you are a woman of child-bearing potential, you will need to have a pregnancy test.
Day 1 of Month 1	<ul style="list-style-type: none"> • If using Zoledronic acid, you will receive an IV infusion at your clinical site. • If using Clodronate, begin taking until the end of study, unless told to stop by your health care team. • If using Ibandronate, begin taking until the end of study, unless told to stop by your health care team.
Day 1 of Months 2-6 and Months 9, 12, 15, 18, 21, 24, 27, 30, 33 and 36	<ul style="list-style-type: none"> • Get kidney function test.
Day 1 of Months 2, 4, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, and 36	<ul style="list-style-type: none"> • Get routine blood tests (including kidney function test). • Return to your doctor's office at _____ (insert appointment time) for your next physical

	examination.
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Day	What you do (contd.)
Within 14 days of end of treatment	<ul style="list-style-type: none"> Return to your doctor's office at _____ (insert appointment time) for your next physical examination Get bone scan.
Within 3 months before or after completing study	<ul style="list-style-type: none"> Get routine dental examination.
After completing study, every 6 months for 5 years, then annually until year 10 or until death	<ul style="list-style-type: none"> Return to your doctor's office at _____ (insert appointment time) for your next physical examination

Study Plan

Another way to find out what will happen to you during the study is to read the chart below. Start reading at the top and read down the list, following the lines and arrows.



When you are finished taking study drugs...

You will need to see your study doctor for a physical examination and bone scan. Additionally, you will need to have a dental examination within 6 months of completing treatment or being removed from study.

How long will I be in the study?

You will be asked to take bisphosphonates for 3 years. After you are finished taking bisphosphonates, the study doctor will ask you to visit the office for follow-up exams every year for a length of ten years. The follow-up evaluation tests that are standard to cancer care will include a medical history, physical examination, and performance status.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the zoledronic acid, clodronate, or ibandronate can be evaluated by your doctor. Another reason to

tell your doctor that you are thinking about stopping is to discuss what followup care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the zoledronic acid, clodronate, or ibandronate. In some cases, side effects can be serious, long lasting, or may never go away.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks and side effects related to the zoledronic acid include the following:

Likely

- **Fever**
- **Nausea**
- **Constipation**
- **Shortness of breath**
- **Low red blood cell counts which may cause fatigue or pale appearance**
- **Loss of appetite**
- **Muscle or bone pain**

Less Likely

- **Vomiting**
- **Diarrhea**
- **Alteration of serum calcium and phosphate levels in your blood (This can result in numbness and tingling sensations in the fingers and toes, muscle cramps, irritability or depression, seizures, symptoms of heart failure, and anemia.)**
- **Joint pain, arthritis**
- **Bone pain/tingling**
- **Rash**
- **Abdominal pain**
- **Swelling of the legs**
- **Cough**
- **Headache**
- **Dizziness**
- **Insomnia**
- **Depression**
- **Anxiety**
- **Confusion**

Rare, But Serious

- **Seizures**
- **Abnormal kidney function or failure**

- Osteonecrosis of the jaw (permanent damage to the jawbone)
- Inflammation of the eyes can occur with zoledronic acid use. Symptoms can include red eye, eye pain, and/or decreased/blurry vision. In some cases, these events did not improve until the zoledronic acid was discontinued.
- Allergic reaction: There have been rare reports of allergic reaction with intravenous zoledronic acid including swelling in the mouth or throat making it difficult to breath. Very rare cases of anaphylactic reaction/shock have also been reported.

Risks and side effects related to the clodronate include the following:

Likely

- Nausea

Less Likely

- Vomiting
- Diarrhea or constipation
- Alteration of serum calcium in your blood (This can result in numbness and tingling sensations in the fingers and toes, muscle cramps, irritability or depression, seizures, and symptoms of heart failure.)
- Rash
- Alterations of liver enzymes in your blood (a possible result of injury to the liver).

Rare, But Serious

- Abnormal kidney function or failure
- Respiratory effects in patients with aspirin-sensitive asthma
- Osteonecrosis of the jaw (permanent damage to the jawbone).

Risks and side effects related to the ibandronate include the following:

Likely

- Diarrhea
- Pain in extremities (arms or legs)
- Upset stomach
- Back pain

Less Likely

- Pain or trouble with swallowing
- Chest pain (non-cardiac)
- Very bad heartburn or heartburn that does not get better
- Low calcium levels in the blood which could cause shakiness and abnormal heart rhythms
- Nausea
- Myalgia (muscle pain)

Rare, But Serious

- Stomach ulcers (hole in the lining of the stomach) which may bleed and be life-threatening
- Increase of symptoms associated with gastroesophageal reflux disease, including difficulty swallowing, inflammation of the esophagus, and development of ulcers within the esophagus
- Osteonecrosis of the jaw (permanent damage to the jawbone)

Reproductive risks: You should not become pregnant while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. Women of child-bearing potential will have a pregnancy test.

Osteonecrosis of the jaw: Recent reports suggest a possible association between the use of intravenous bisphosphonates, such as zoledronic acid, and osteonecrosis of the jaw (permanent damage to the jawbone), a rare, but serious potential side effect. This condition may be painful and may happen after tooth extraction or other dental procedures such as tooth cleaning or when a patient is also getting chemotherapy while taking bisphosphonates. Oral clodronate and ibandronate may also increase the risk of osteonecrosis of the jaw, although this link is not as well established.

Severe bone pain: Rare reports of severe and occasionally disabling bone, joint, and/or muscle pain has been reported with bisphosphonate use. The severe bone, joint, and/or muscle pain may occur within days, months, or years after starting a bisphosphonate. Some patients have reported complete relief of symptoms after discontinuing the bisphosphonate, whereas others have reported slow or incomplete recovery. The risk factors that contribute to severe bone, joint, and/or muscle pain associated with bisphosphonates are unknown.

For more information about risks and side effects, ask the study doctor.

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. While doctors hope zoledronic acid, clodronate, and ibandronate will be more useful against cancer compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help doctors learn more about bisphosphonates as a treatment for cancer. This information could help future cancer patients.

Some small trials of clodronate have suggested some possible benefit for that drug, although with conflicting results, and now a study with zoledronic acid showed benefit for dosing twice a year in pre-menopausal women, with estrogen-receptor positive breast cancer receiving ovarian suppression and not chemotherapy. However, at present, it is not standard of care to give these drugs in the majority of breast cancer patients.

What other choices do I have if I do not take part in this study?

Your other choices may include:

- Getting treatment or care for your cancer without being in a study.
- Taking part in another study involving bisphosphonate treatments.
- Getting no treatment.

There is currently no standard treatment for the prevention of bone metastasis in breast cancer. Talk to your doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if

required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- Local Institutional Review Board (IRB)
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- The Southwest Oncology Group
- Qualified representatives from the drug manufacturers for the three drugs used in this study.

What are the costs of taking part in this study?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

Administration of the drug will be *charged in the usual way*. The parts of the research consisting of keeping research records will be paid by those organizing and conducting the research. The research requires that you receive certain standard medical tests and examinations. These standard tests and examinations will be *charged in the usual way*.

The drug manufacturers, Berlex/Schering and Roche, will provide you with the investigational agents, free of charge for this study. Although zoledronic acid is commercially available, Novartis will provide this drug to you free of charge for this study. If during this study any of these drugs becomes approved for use in your cancer, you and/or your health plan may have to pay for drugs as needed to complete the study.

You will not be paid for taking part in this study.

If you have a severe financial need, lack dental insurance, and do not have access to dental care by any other means, then financial assistance will be available for dental exams.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at <http://cancer.gov/clinicaltrials/understanding/insurance-coverage> . You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, _____, if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at 906-225-3922.

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

A Data Safety and Monitoring Board, an independent group of experts, will be reviewing the data from this research throughout the study. We will tell you about important new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ at 906-225-3922.

For questions about your rights while taking part in this study, call the Patient Advocate at 906-225-3433.

Please note: This section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be a part of the main study even if you say ‘no’ to taking part in any of these additional studies.

Future Contact

I agree to allow my study doctor, or someone approved by my study doctor, to contact me regarding future research involving my participation in this study.

Yes No

You can say "yes" or "no" to each of the following studies. Please mark your choice for each study.

I agree to submit a tissue specimen for the analysis of the substance parathyroid hormone related protein (PTHrP) to see if this predicts the risk of my breast cancer spreading to the bones. This is an experimental test that may indicate a higher chance that breast cancer has spread to the bones. Since the significance of this test is not proven, neither you nor your doctor will be given the results of this test.

YES NO

I agree to submit a blood sample to be analyzed for the substance n-telopeptide to see if high levels will predict the risk of my breast cancer spreading to the bones. This is an experimental test that may indicate a higher chance that breast cancer has spread to the bones. Since the significance of this test is not proven, neither you nor your doctor will be given the results of this test.

YES

NO

Should any tissue or blood remain from these studies, we would like to store your specimens for future research studies. The remaining sections of the informed consent document apply to specimens for research purposes.

Consent Form for Use of Specimens for Research

Where will my specimens be kept?

Southwest Oncology Group Solid Tumor Tissue Bank:
University of Colorado HSC at Fitzsimons
RC-1 South, Room L18-5400A
12801 East 17th Avenue
Aurora, CO 80045
Phone: 303/724-3086

About Using Specimens for Research

We would like to keep leftover tissue and serum for future research. If you agree, these specimens will be kept and may be used in research to learn more about cancer and other diseases. Please read the information sheet called "How Are Specimens Used for Research" to learn more about specimen research.

Your specimens may be helpful for research whether you do or do not have cancer. The research that may be done with your specimens is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your specimens will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Things to Think About

The choice to let us keep the left over specimens for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your specimens can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your specimens. Then any specimens that remain will no longer be used for research.

In the future, people who do research may need to know more about your health. While the Southwest Oncology Group may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes specimens are used for genetic research (about diseases that are passed on in families). Even if your specimens are used for this kind of research, the results will not be put in your health records.

Your specimens will be used only for research and will not be sold. The research done with your specimens may help to develop new products in the future.

Benefits

The benefits of research using specimens include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No". If you have any questions, please talk to your doctor or nurse, or call our research review board at IRB's phone number.

No matter what you decide to do, it will not affect your care.

1. **My specimens may be kept for use in research to learn about, prevent, or treat cancer.**
Yes No
2. **My specimens may be kept for use in research to learn about, prevent, or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).**
Yes No
3. **Someone may contact me in the future for my permissions to allow other uses of my specimens.**
Yes No

If you decide to withdraw your specimens from a Southwest Oncology Group Specimen Repository in the future, a written withdrawal of consent should be submitted through your treating physician to the Southwest Oncology Group Operations Office. If you decide to withdraw your permission from the banking part of the study, your tissue will be returned to the treating institution, and any remaining blood specimens will be destroyed.

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at <http://cancer.gov/>

- For NCI's clinical trials information, go to: <http://cancer.gov/clinicaltrials/>
- For NCI's general information about cancer, go to <http://cancer.gov/cancerinfo/>

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Specimen Consent Supplemental Sheets

How are Specimens Used for Research?

Where do specimens come from?

A specimen may be from a blood sample or from bone marrow, skin, toenails or other body materials. People who are trained to handle specimens and protect donors' rights make sure that the highest standards of quality control are followed by the Southwest Oncology Group. Your doctor does not work for the Southwest Oncology Group, but has agreed to help collect specimens from many patients. Many doctors across the country are helping in the same way.

Why do people do research with specimens?

Research with specimens can help to find out more about what causes cancer, how to prevent it, how to treat it, and how to cure it. Research using specimens can also answer other health questions. Some of these include finding the causes of diabetes and heart disease, or finding genetic links to Alzheimer's.

What type of research will be done with my specimen?

Many different kinds of studies use specimens. Some researchers may develop new tests to find diseases. Others may develop new ways to treat or even cure diseases. In the future, some of the research may help to develop new products, such as tests and drugs. Some research looks at diseases that are passed on in families (called genetic research). Research done with your specimen may look for genetic causes and signs of disease.

How do researchers get the specimen?

Researchers from universities, hospitals, and other health organizations conduct research using specimens. They contact the Southwest Oncology Group and request samples for their studies. The Southwest Oncology Group reviews the way that these studies will be done, and decides if any of the samples can be used. The Southwest Oncology Group gets the specimen and information about you from your hospital, and sends the specimen samples and some information about you to the researcher. The Southwest Oncology Group will not send your name, address, phone number, social security number or any other identifying information to the researcher.

Will I find out the results of the research using my specimen?

You will not receive the results of research done with your specimen. This is because research can take a long time and must use specimen samples from many people before results are known. Results from research using your specimen may not be ready for many years and will not affect your care right now, but they may be helpful to people like you in the future.

Why do you need information from my health records?

In order to do research with your specimen, researchers may need to know some things about you. (For example: Are you male or female? What is your race or ethnic group? How old are you? Have you ever smoked?) This helps researchers answer questions about diseases. The information that will be given to the researcher may include your age, sex, race, diagnosis, treatments and family history. This information is collected by your hospital from your health record and sent to the Southwest Oncology Group. If more information is needed, the Southwest Oncology Group will send it to the researcher.

Will my name be attached to the records that are given to the researcher?

No. Your name, address, phone number and anything else that could identify you will be removed before they go to the researcher. The researcher will not know who you are.

How could the records be used in ways that might be harmful to me?

Sometimes, health records have been used against patients and their families. For example, insurance companies may deny a patient insurance or employers may not hire someone with a certain illness (such as AIDS or cancer). The results of genetic research may not apply only to you, but to your family members too. For

disease caused by gene changes, the information in one person's health record could be used against family members.

How am I protected?

The Southwest Oncology Group is in charge of making sure that information about you is kept private. The Southwest Oncology Group will take careful steps to prevent misuse of records. Your name, address, phone number and any other identifying information will be taken off anything associated with your specimen before it is given to the researcher. This would make it very difficult for any research results to be linked to you or your family. Also, people outside the research process will not have access to results about any one person, which will help to protect your privacy.

VOLUNTARY CONSENT:

You certify that you have read the preceding or it has been read to you and that you understand its contents. Any questions you have pertaining to the research or research related injuries have been and will be answered by Dr. _____ or his/her associates, who may be reached by phoning the office at (906) 225-3922. During evenings, weekends, or holidays you may phone Marquette General Hospital at (906) 228-9440, and request to speak with the medical oncologist on call. Any questions you have concerning your rights as a research subject will be answered by the Patient Advocate at Marquette General Hospital, who may be reached by phoning (906) 228-9440. You will be given a copy of this consent form.

Your signature below means that you have freely agreed to participate in this investigational study.

Patient's Signature

Date

Signature of person conducting
Informed consent discussion

Date

I certify that the nature and purpose, the potential benefits, and possible risks associated with participation in this research study have been explained to the patient indicated, and that any questions about this information have been answered.

Investigator's Signature

Date

Your signature below means that you do not wish to participate in this investigational study.

Patient's Signature

Date

Signature of person conducting
Informed consent discussion

Date

Investigator's Signature

Date

IRB approved consent form 8/8/07
IRB approved Amend. #2 08/13/2008
IRB approved Revision #4 10/08/2008