

**CONSENT AND AUTHORIZATION FORM
FOR INSTITUTIONAL REVIEW BOARD APPROVED HUMANITARIAN USE
DEVICE**

**Study Title: TREATMENT OF UNRESECTABLE HEPATOCELLULAR CARCINOMA
WITH THERASPHERE®
(YTTRIUM-90 GLASS MICROSPHERES):
An HDE Treatment Use Protocol**

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INVITATION TO PARTICIPATE: You have been invited to participate in this treatment protocol because you have a primary cancer of the liver (hepatoma). Surgical removal of the tumor is not possible because of the location and/or extent of your tumor.

PURPOSE: The purpose of this protocol is to provide access to TheraSphere® treatment for patients with liver cancer who cannot be treated by surgical removal of the affected part of the liver. Patient response and any side effects of TheraSphere® treatment will be examined. This protocol will provide supervised and limited access to TheraSphere® treatment at this hospital. Your participation in this treatment protocol is strictly voluntary. This is not a research study and there are no comparison or experimental treatments being used.

TheraSphere® is a medical device containing yttrium-90 (Y-90), a radioactive material that has been used previously in the treatment of liver tumors. When Y-90 is incorporated into very tiny glass beads (TheraSphere®), it can be injected into the liver through the blood vessels supplying the liver, thereby allowing a large local dose of radiation to be delivered to the tumor with less risk of toxic effects from radiation to other parts of the body or to healthy liver tissue. The radiation from TheraSphere® is contained within the body and becomes minimally active within 7 days after treatment due to physical decay (*see package insert*). The glass beads remain in the body, but do not cause any health problems. TheraSphere® has been approved for use in the treatment of liver cancer in Canada and has been approved for humanitarian use for liver cancer in the United States by the Food and Drug Administration. A Humanitarian Use Device (HUD) is a device intended to benefit patients in the treatment or diagnosis of diseases or conditions that affect fewer than 4,000 individuals in the United States per year. A HUD has been judged “safe” by the FDA, but its “efficacy “ is not known.

PROCEDURES: If you agree to participate, you will receive treatment with TheraSphere® if you meet the eligibility criteria that define who may safely be treated with this medical device. There are no

other treatments being evaluated in this use study. If it is found that you are eligible to receive TheraSphere® treatment after you consent to participate, the study doctor will determine if you want to receive a standard alternative liver-directed treatment. Also, treatment with TheraSphere® does not prevent you from being able to receive other treatments for your liver cancer after TheraSphere® therapy. All visits and procedures related to TheraSphere® treatment are performed in the outpatient setting.

If you consent to participate, you may have the following procedures performed to make an initial evaluation of your eligibility for this treatment: physical examination, medical history, blood tests requiring approximately 2 tablespoons of blood, a chest x-ray, CT or MRI scan to examine your lungs, and an imaging study (CT or MRI scan) of your abdomen to evaluate your liver, stomach and intestines. These procedures may require one or two visits, depending on your schedule and the appointments available for the necessary studies.

Based on the results of these screening tests, it may be determined that you are not eligible to proceed with TheraSphere® treatment. In this event, the study doctor will provide you with an explanation of the findings that led to this decision and the treatment alternatives that are available.

The study doctor will develop a plan for your treatment with TheraSphere® and discuss it with you. Depending on the size and distribution of your liver cancer, the treatment plan may include more than one treatment with TheraSphere® to reach all areas of the liver containing tumor. Repeat treatment is performed approximately one month after the initial treatment.

If you are eligible based on the initial screening, you will proceed to the second stage of screening. Approximately two weeks before the first planned treatment, you will have a small tube (catheter) inserted through a small incision in the skin of your inner thigh and into a blood vessel in your leg. The catheter will be pushed within this vessel and placed into a blood vessel leading to the liver. Several tests will be done to confirm that you can safely receive this treatment. These tests include an x-ray study of the blood supply to your liver that uses a contrast agent to highlight the blood vessels (liver angiogram) and a nuclear medicine study that uses a radioactive tracer substance to display the blood flow to your lungs, stomach, and intestines (Tc-99m MAA Scan). These studies will take about 2 hours to complete and allow the study doctor to confirm whether TheraSphere® can be delivered safely to the affected areas of your liver with minimal risk of exposure of other 'innocent by-stander' body organs to the radioactivity released from the TheraSphere®.

If it is determined from these tests that you are eligible, the study doctor will develop a plan for your treatment with Therasphere® and discuss it with you. Depending on the size and distribution of your liver cancer, the treatment plan may include more than one treatment with Therasphere® to reach all areas of the liver-containing tumor. Repeat treatment is performed approximately one month after the initial treatment. The study doctor will order the required dose of TheraSphere® and schedule a day for your first treatment.

If it is determined from these tests, that you cannot be treated with TheraSphere®, you can decide with your doctor whether you want to receive another standard type of liver-directed cancer therapy at this time. Your doctor will discuss the alternative therapy plan with you before the day of treatment. If you do not receive TheraSphere® treatment, your participation in the treatment protocol will end and no further evaluations will be required.

To deliver TheraSphere®, or any other liver-directed cancer therapy, it is necessary to place a very fine hollow tube, called a catheter, into the hepatic artery to provide a means of delivering the treatment. If you already have such a catheter in place, it will be used to deliver the TheraSphere® treatment. If you do not have this kind of catheter, the study doctor will decide to either place a permanent catheter, which would be done during a surgical procedure, or to place a temporary catheter, which would be done by a skilled radiologist in the X-ray Department.

Once this catheter is in place, and the pre-treatment imaging studies have confirmed that you are eligible to receive TheraSphere® treatment, the TheraSphere® will be injected through the catheter, followed by a flushing solution of normal saline. After treatment, you will remain at the hospital for several hours, until your doctor determines that you are sufficiently recovered to return home. The radiation emitted by TheraSphere® is confined within your body and is relatively short-acting. No special isolation procedures are required after treatment. If you experience any serious problems or complications during or immediately after treatment, you may be admitted to the hospital for further observation and management of the problem. When you leave the hospital, you will be provided with a telephone number that will reach a study doctor at any time of the day or night, if you experience any problems after the procedure.

If you are treated with TheraSphere®, you will be asked to return to the hospital one month after each treatment for a follow-up examination to see how you are doing. The study doctor will decide what tests should be repeated at this time to determine how you are responding to TheraSphere® treatment. These tests may include, among others: physical examination, clinical interview to assess how you are feeling, blood tests, and CT or MRI scan of the abdomen to evaluate tumor response. These procedures are all a part of usual clinical care for treatment of liver cancer.

After the final visit (30 days after last treatment), your referring oncologist (cancer specialist) will direct further clinical care related to your liver cancer. The study doctor will continue to communicate with your doctor at least once a year for up to two years to review how you are doing.

RISKS: Participation in this treatment protocol involves some known risks, discomforts or inconvenience. There also may be risks that are unknown or unforeseeable.

Risks of Catheter Placement: The possible side effects include pain at the insertion site, possible risk of clotting of the artery, or bleeding around the catheter insertion site. There is a very small chance (3%) that the hepatic artery might develop an obstructing clot that would temporarily result in pain in the liver and increased abnormalities in liver function blood tests. If a clot occurs, standard treatments to dissolve or remove the clot will be administered.

Risk of Venipuncture: The risks of drawing blood include possible fainting, bleeding and infection, and rarely, nerve damage.

Risks of Tc-99m Macroaggregated Albumin (MAA) Study: This is a standard diagnostic procedure that has minimal health risks. The radioactive tracer substance (Tc-99m MAA) that is injected into the blood vessels remains active in the body for a short time, after which it is eliminated through the kidneys.

Risks of TheraSphere® Treatment: Before any treatment is given, you will undergo a special liver x-ray study to find out whether TheraSphere® can be delivered safely to the affected areas of your liver with minimal risk of exposure of other body organs to the radioactivity released from TheraSphere®. If

there is evidence of blood circulation from the liver to organs outside the liver that is not correctable and that could result in exposure of these organs to unnecessary radiation, you will not be given treatment with TheraSphere®. Even after this safety screening evaluation, there is still a small risk that radiation could potentially be delivered to your lungs and/or digestive tract, resulting in either lung damage, which could include fluid retention (edema), scarring (fibrosis), and could result in shortness of breath; or irritation of the gastrointestinal tract, which could result in chronic pain, nausea, vomiting, ulceration, and bleeding.

After TheraSphere® treatment, you may experience some abdominal pain, nausea, vomiting, and/or occasional fever. Treatment of nausea and vomiting would consist of antacids or anti-vomiting medications. Treatment for fever would include use of anti-fever drugs, such as Tylenol or Ibuprofen. TheraSphere® releases radiation that affects both cancerous and non-cancerous liver tissue. As a result, there may be changes in your liver function blood tests for 2 to 3 weeks' after treatment. The study doctor will decide how frequently blood tests are needed to evaluate the effects of TheraSphere® on your blood counts and liver function.

Your physician will be checking you closely to see if any of these side effects are occurring. Post-treatment follow-up visits will be scheduled to monitor any side effects that occur. Many side effects disappear shortly after the delivery of treatment. Other side effects may be longer lasting or permanent. Your doctor may prescribe medication to minimize these side effects. You should understand that treatment to help control side effects could result in added costs.

FERTILITY/REPRODUCTIVE ISSUES: If you are a woman capable of child-bearing, you will undergo a pregnancy test prior to receiving TheraSphere® treatment. The results will be made known to you. You should not become pregnant while being treated with TheraSphere®, and you are asked to use a medically-accepted form of birth control (such as oral contraceptives, barriers, surgical sterility, or abstinence) while under treatment, until you are at least 30 days past your last TheraSphere® treatment. Women who are pregnant are excluded from this study, and if you find that you have become pregnant while participating, you agree to notify your doctor immediately.

If you are a man, you agree to use a means of birth control (such as condoms, abstinence, vasectomy) while you are taking part in this study, because the effect of the TheraSphere® treatment on your sperm or upon the development of an unborn child are unknown. You are asked to agree not to father any children while on this study.

BENEFITS: The possible benefits of this treatment are shrinkage of your tumor and prolongation of your life. It is not possible to predict whether or not any personal benefit will result from your participation in this study. There is the possibility that you will get no direct benefit from your participation.

ALTERNATIVES: There are alternate forms of therapy for liver cancer that you may or may not already have received. Other forms of liver-directed therapy, using embolization (blockage of blood supply to the tumor) alone, or embolization in combination with other anti-cancer drugs or toxic chemicals (chemoembolization or CE) is one alternative form of treatment and can be used before or after TheraSphere® treatment. CE also requires placement of a catheter. Other risks of CE include pain, nausea and vomiting, and severe liver failure. There is no radiation risk with CE. Tumor response rates to CE vary widely and have been reported to range from 40-90%.

External radiation therapy to the liver may reduce symptoms, but only 20% of patients experience significant tumor shrinkage. Systemic chemotherapy is of little value in liver cancer, with response rates ranging from 6-19%. Liver transplantation has curative potential, but is limited by stringent requirements for organ recipients and limited donor organ availability. A final alternative is no therapy at all. Your study doctor will explain the advantages and disadvantages of alternative treatments that are being used for this disease.

You can still receive other therapies after TheraSphere® treatment.

COSTS AND FINANCIAL RISKS: You are encouraged to discuss the possible effects of the costs associated with this treatment with the study doctor. Under this treatment protocol, all of the required procedures are considered standard care for your disease. These include physician visits, outpatient hospital costs, physician fees for catheter placement, laboratory tests, and radiologic studies (x-rays, MRI, CT scans) that are necessary to insure safety and to check for response to treatment. If your insurance company does not pay for these procedures, you will be responsible for their cost. The study doctor will discuss the possible effects of these costs with you. TheraSphere® (MDS Nordion, Inc.) is an approved product and should be covered by third party payers, although it is difficult to predict which payers will cover what costs in all instances. Every effort will be made to establish which costs will or will not be covered by your insurance policy prior to enrollment in this treatment study.

COMPENSATION: There will be no financial compensation for participation in this treatment study.

CONFIDENTIALITY: A record of your progress will be kept in a confidential file at this hospital. However, your medical records and any slides or tissue specimens collected as part of your diagnosis and treatment for liver cancer at this hospital, may be examined by the study doctor, by members of the Food and Drug Administration (FDA), by MDS Nordion, the manufacturer of TheraSphere® or their contracted auditors.

After completion of your treatment, you are asked to give permission for the study doctor to contact you or your oncologist to obtain information about your health status for a period up to two years after treatment ends. All information so collected will be kept confidential.

AUTHORIZATION TO USE AND DISCLOSE PROTECTED HEALTH INFORMATION

You hereby authorize Legacy Health System to use and disclose your Protected Health Information (PHI) solely for the purposes of the Research Study. PHI includes any portion of your medical records that could be used to identify you such as name, address, birth date, etc.

You are free at any time to restrict Legacy Health System's use and disclosure of your PHI, for purposes unrelated to the Research Study, without penalty or other consequence. However, you may be denied participation in, or continued participation in, this Research Study if at any time you choose to restrict Legacy Health System's use and disclosure of Health Information that is necessary for the completion of the Research Study described in this Consent Form.

Authorized Persons and Recipients

You hereby authorize the Legacy Health System to use and disclose your PHI to the following (eg. person(s) or class(es) of persons:

- The study sponsor (MDS Nordion) or its representatives, including companies it hires to provide study-related services
- Researchers who are conducting this study at other study centers

- The Legacy Institutional Review Board (ethics committee) that approved this study and any other committees responsible for overseeing the research

Government health agencies (such as the Food and Drug Administration) in the US or other countries

Expiration Date

You hereby authorize Legacy Health System to use and disclose your PHI in accordance with the terms and conditions of this Consent Form indefinitely.

Re-Disclosures to Third Parties

Once Legacy Health System discloses PHI to the Recipient(s) identified above, Legacy Health System cannot guarantee that Recipient(s) will not re-disclose PHI to other persons who may not be bound by this Consent Form, or otherwise be permitted to use or disclose PHI in ways that you did not intend.

Withdrawal of Authorization to use and Disclose Protected Health Information

You may decline at any time to participate in any or all of these follow-up activities. If you choose not to participate, it will not affect your medical treatment, nor is there a penalty or loss of benefits to which you would otherwise be entitled. You may change your mind and revoke this authorization at any time. To revoke this authorization, you must write to:

Jason Bauer, MD
Diagnostic Imaging Northwest
2701 N. Vaughn Street, Suite 425
Portland, OR 97210

However, if you revoke this authorization, you may no longer be able to participate in the study. In addition, even if you revoke the authorization, the information already obtained by Legacy Health System and MDS Nordion may be used and disclosed as permitted by this authorization and this informed consent. By signing this form you have not given up any of the legal rights which you otherwise would have as a participant in a research study.

ADDITIONAL INFORMATION: You will be kept informed of the progress of clinical experience with TheraSphere® for treatment of liver cancer. While you are a participant on this treatment protocol, you will be informed of any new findings that might affect your willingness to continue with this treatment or future clinical care for liver cancer.

DISCLAIMER/WITHDRAWAL: Your participation in this treatment protocol is completely voluntary and you may withdraw at any time without prejudicing your present or future care. You also understand that if you withdraw from the protocol, you will continue to receive medical care and clinical data will be collected from your medical records with your written permission at that time. If you permit the collection of these data, it will be noted in your chart and medical records.

There are circumstances under which the study doctor might be required to discontinue your participation, whether you agree or not. These circumstances include: your tumor getting worse despite the treatment or the occurrence of unacceptable side effects after initial treatment. At any time during the 30-day post-treatment follow-up period, if your disease gets worse, you will be taken off-study and your doctor may provide other treatment. If you receive any TheraSphere® and have to discontinue participation early, you will be asked to provide permission for the study doctor to make an annual assessment of your medical record until 24 months post-treatment to determine your health status.

Should your liver cancer progress, should side effects of treatment be severe, or if your physician feels that continuing TheraSphere® treatment is no longer in your best interest, your participation will be discontinued and further treatment options discussed.

INJURY/COMPLICATIONS: Complications may arise during the course of therapy, either due to your liver cancer or due to the treatment. You have been advised that therapy for any such complications will be carried out by your doctors and the costs associated with such care may be provided by third party payers. You have been advised that no compensation for injury will be provided to you as a result of your participation in this treatment protocol.

If you become sick or injured by participation in this treatment, medical treatment will be provided including first aid, emergency treatment and follow-up care as needed. By providing or making available medical treatment for injuries or illness, Legacy Health System and persons conducting this treatment are not admitting fault for injury or illness.

CONTACTS:

If at any time you feel that you have not been adequately informed as to the risks, benefits, alternative procedures, or your rights as a research subject, or feel under duress to participate against your wishes, you can contact Legacy Health System's Research Regulatory Specialist who will be available to speak with you during normal working hours (8:30 a.m. to 5:00 p.m.) at (503) 413-2474.

In the event of injury or illness, you should seek medical attention and contact: Dr. Bauer at (503) 413-7367.

You also understand that if you have any questions pertaining to your participation in this treatment protocol, you may contact the study doctor by calling the telephone numbers listed on page one.

You have been given the opportunity to discuss the above information with your doctor and ask questions and have had these questions answered to your satisfaction.

RADIATION CONSIDERATIONS: This procedure uses radioactive materials (x-rays) and you will receive a radiation exposure. There is a risk associated with this exposure that is justified by your disease. The dose of ionizing radiation in TheraSphere® is designed to be lethal to the cancer cells in your liver. Diversion of part of this dose to your lungs, stomach or intestine also could be lethal. The specific dose you receive will be carefully calculated to be the minimum dose required based on the size of your liver (as measured from CT or MRI images) and the distribution and extent of your tumor. Every effort will be made to prevent flow of the radioactive material to other organs of the body. The type of radioactive material (Yttrium-90) used in TheraSphere® has a short range of tissue penetration (less than 1.5 cm) and becomes minimally active in the body within 7 days after treatment due to physical decay (refer to package insert). There is no need for you to be isolated when you have been treated with TheraSphere® because the radiation is fully contained within the liver.

1. The radiation doses you will receive as a result of participating in this study includes radiation from the administration of 3 gigabecquerel (GBq) or 81 millicurie (mCi), 5 GBq (135 mCi), 10 GBq (270 mCi) or 20 GBq (540 mCi) of TheraSphere®. The additional radiation exposure from the Tc-99m MAA study and from the x-ray studies of the liver blood supply (liver angiography) are within the acceptable limits for diagnostic studies

involving radioactive materials and are routinely used in medicine. The additional risk of this radiation exposure is very small compared to the seriousness of your disease.

2. Using the standard way of describing radiation dose, you will receive 8,000 - 15,000 rad to your liver, a maximum of 3,000 rad to your lungs; other organs and tissues may receive lesser doses, as indicated in the above paragraph under *Radiation Considerations*.
3. Please be aware that this radiation exposure is necessary for this treatment. The Legacy Health System Radiation Safety Committee, a group of experts on radiation matters, has reviewed the use of radiation in this application and has approved this use as being necessary for the treatment.
4. The potential long-term risk from these radiation doses is uncertain, however, as long as the radiation is confined to your liver and lungs (as described under *Risks of TheraSphere® Treatment* above) the side effects are mild to moderate. Any additional risk of this radiation procedure is very small compared to the seriousness of your disease.
5. Please advise your doctor if you have participated in research studies at any hospital or other institutions that involved the use of radiation so that it may be determined that the total radiation dose from all studies is not excessive. Examples of such studies include x-ray studies conducted in radiology departments, cardiac catheterization, and fluoroscopy as well as nuclear medicine studies, e.g., technetium and PET scans.

CONCLUSION: You have read and understand the information in this consent form. You agree to participate in this treatment protocol. Upon signing below, you will receive a copy of the consent form.

Name of Patient

Patient's Signature

Date

Name of Witness

Witness's Signature

Date

Name of Doctor

Doctor's Signature

Date