NRG ONCOLOGY

NRG-HN002

(ClinicalTrials.gov NCT #: **02254278***)*

A RANDOMIZED PHASE II TRIAL FOR PATIENTS WITH p16 POSITIVE, NON-SMOKING ASSOCIATED, LOCOREGIONALLY ADVANCED OROPHARYNGEAL CANCER

Amendment 3: December 20, 2017

NRG ONCOLOGY
NCI Protocol NRG-HN002
Consent Form

Study Title for Study Participants: Testing less intensive treatment for selected low-risk patients with oropharyngeal cancer

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: A Randomized Phase II Trial for Patients with p16 Positive, Non-Smoking Associated, Locoregionally Advanced Oropharyngeal Cancer

What is the usual approach to my cancer?

You are being asked to take part in this study because you have oropharyngeal cancer of a specific type that appears to be more sensitive to radiation treatment. People who are not in a study are usually treated with high doses of radiation and chemotherapy. For patients who receive the usual approach for this cancer, about 85 out of 100 are alive and free of cancer at five years. These treatments can result in many side effects both during and after treatment. Your doctor will discuss these with you.

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

If you decide not to take part in this study, you have other choices. For example:

- you may choose to have the usual approach described above
- you may choose to take part in a different study, if one is available
- or you may choose not to be treated for cancer but you may want to receive comfort care to relieve symptoms.

Why is this study being done?

Previous studies of your type of cancer have shown high rates of cancer control but result in many short and long term side effects when treated with high dose radiation and chemotherapy. Recently, investigators have noticed similar high rates of cancer control in small numbers of patients who receive less intensive treatments using lower doses of radiation with or without chemotherapy. It is expected that the side effects of treatment with lower doses of radiation would be less. For this reason this study is looking at two different ways of reducing the intensity of your treatment.

The purpose of this study is to compare any good and bad effects of using lower dose radiation therapy and chemotherapy to using lower dose radiation therapy alone. This study will allow the researchers to know whether these different approaches are better, the same, or worse than the usual approach. To be better, the study approach should result in the same survival rate of the usual approach (about 85 out of 100 patients alive and free of cancer at five years) but with less long term side effects.

There will be about 296 people taking part in this study.

What are the study groups? (4/29/15)

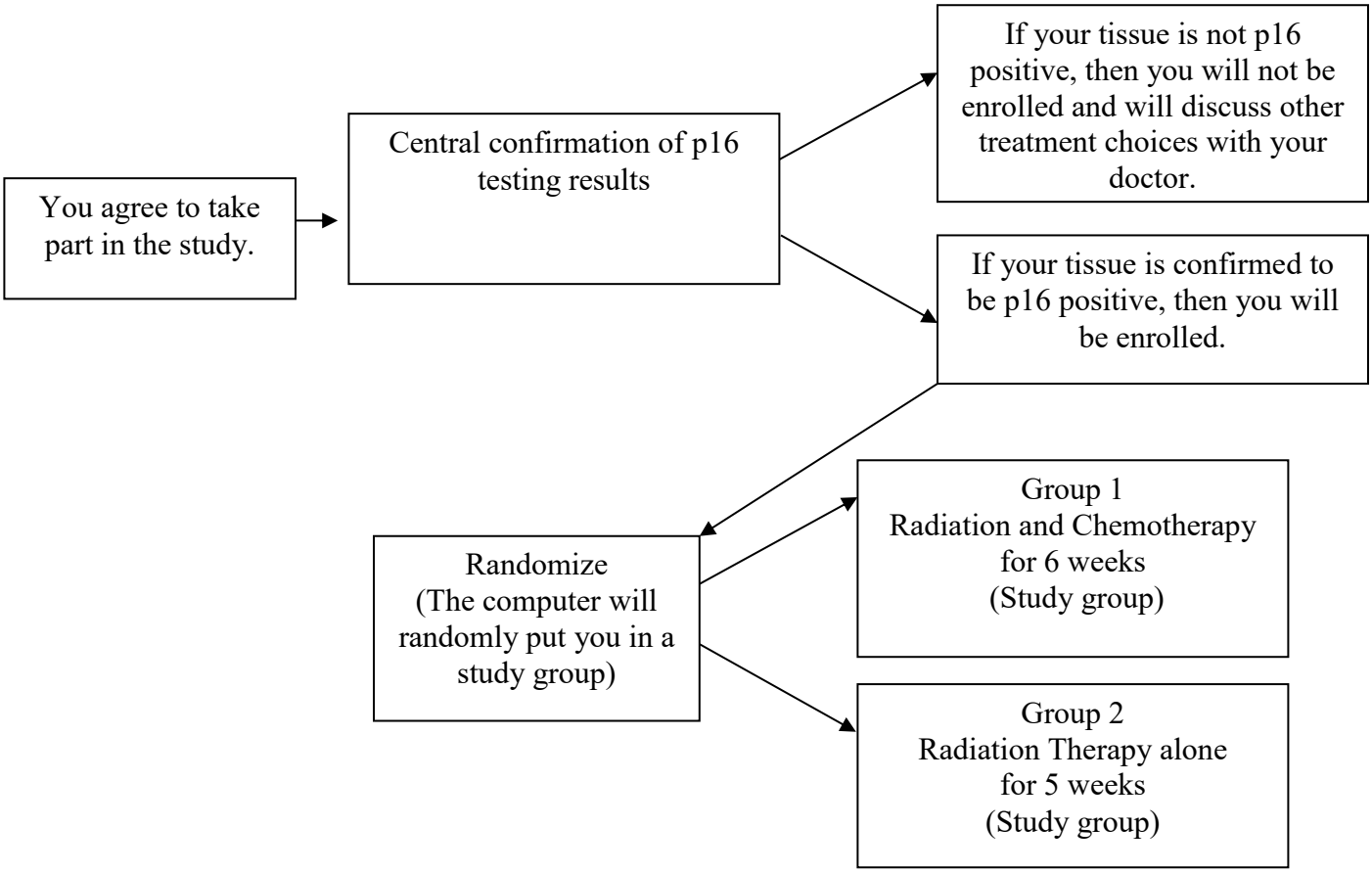
This study has two study groups.

Group 1 will receive radiation therapy once a day, 5 days a week (for a total of 60 Gy over 6 weeks) and chemotherapy, cisplatin, (given through the vein for about 30-60 minutes) once a week for 6 weeks. Medications and saline solutions to prevent side effects of chemotherapy may also be given by vein and may prolong your time in the chemotherapy clinic to as much as 4-6 hours.

Group 2 will receive radiation therapy alone in a schedule of 6 treatments a week (radiation is accelerated compared to Group 1) for a total of 60 Gy over 5 weeks. The 6th treatment can be either given on a Saturday or 2 treatments can be given on one week day, 6 hours apart, as long as the radiation is completed within 5 weeks.

A computer will by chance assign you to treatment groups in the study. This is called randomization. This is done by chance because no one knows if one study group is better or worse than the other. You will have an equal chance of being placed in either group.

Another way to find out what will happen to you during this study is to read the chart below. Start reading at the left side and read across to the right, following the lines and arrows.



How long will I be in this study? (4/29/15)

Group 1 patients will receive radiation and chemotherapy for 6 weeks. Group 2 patients will receive radiation for 5 weeks. After you finish treatment, your doctor will continue to watch you for side effects, check your disease, and see you in follow-up visits at 1 month after treatment, every 3 months for years 1 and 2, every 6 months for years 3, 4, and 5, then once a year for your lifetime.

What extra tests and procedures will I have if I take part in this study?

Most of the exams, tests, and procedures you will have are part of the usual approach for your cancer. However, there are some extra tests, and procedures that you will need to have if you take part in this study.

1. Your privacy is very important, and the researchers will make every effort to protect it. Your test results will be identified by a unique code, and the list that links the code to your name will be kept separate from your samples and health information. Your test results will be available to your doctor. If any of your tissue is left over from this extra test, it will be stored for biobanking, if you agree. There is more information about biobanking in the optional study section.
2. Before you begin the study, you are required to fill out a form with questions about your swallowing abilities. It will take you 5-10 minutes. If you can't fill out the form because it is not available in your language, you can still take part in the study.
3. Before beginning the study, women who can have children must have a negative pregnancy test in order to take part. The radiation therapy (and for group 1 patients, the chemotherapy) used in this study could be very damaging to an unborn baby.

What possible risks can I expect from taking part in this study? (5/17/16)

If you choose to take part in this study, there is a risk that:

- The study approach may not be better, and could possibly be worse, than the usual approach for your cancer.
- You may lose time at work or home and spend more time in the hospital or doctor's office than usual
- You may be asked sensitive or private questions which you normally do not discuss

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.

The tables below show the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Possible Side Effects of Cisplatin (Table Version Date: May 28, 2013)

COMMON, SOME MAY BE SERIOUS In 100 people receiving Cisplatin, more than 20 and up to 100 may have:
• Nausea, vomiting • Infection, especially when white blood cell count is low • Anemia, which may cause tiredness, or may require blood transfusions • Bruising, bleeding • Kidney damage, which may cause swelling, may require dialysis • Hearing decrease, including ringing in ears • Numbness, tingling, or pain of the arms and legs

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Cisplatin, from 4 to 20 may have:
• Allergic reaction, which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Confusion • Difficulty with balance

RARE, AND SERIOUS In 100 people receiving Cisplatin, 3 or fewer may have:
• Cancer of bone marrow later in life caused by chemotherapy • Seizure

Possible risks from exposure to radiation as a result of the tests required to understand the extent of your head and neck cancer and to check the response of your disease to therapy:

The following possible risks apply to all patients who are tested and receive the usual treatment for their head and neck cancer, whether they take part in this study or not. All patients that are being treated with modern radiotherapy and are being followed for their head and neck cancer will be exposed to the doses of radiation described below. Overall, the doses of radiation that are being discussed below are very small compared to those that will be delivered to head and neck chest as part of the usual radiotherapy treatment.

Possible Side Effects of Research Radiation Therapy

COMMON, SOME MAY BE SERIOUS In 100 people receiving radiation therapy, more than 20 and up to 100 may have:
• Reddening, tanning, or peeling of the skin, which may be permanent • Mild pain • Hair loss in the area of radiation, which may be permanent • Tiredness • Weight loss • Sores in the mouth and throat, which may be painful especially when swallowing • Cavities, tooth decay, loss of teeth, tooth sensitivity • Dry mouth, changes in taste, thick saliva, reduced sense of smell—may be permanent • Pain or pressure in the ear

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving radiation therapy, from 4 to 20 may have:
• Decrease in function of the thyroid gland that may require you to take thyroid replacement medicine • Damage to the nerves of the shoulder and arm, which may cause decreased movement and feeling • Ear infection • Hearing loss • Difficulty swallowing, which may require a long term or permanent feeding tube

RARE, AND SERIOUS In 100 people receiving radiation therapy, 3 or fewer may have:
• Breathing and swallowing problems that may require a surgical procedure to create an opening through the neck into the windpipe • Damage to the nerves in the head and neck that control sensation, expression, or other motor functions • Damage to the jawbone, which may cause jaw pain and loosening of teeth • Damage to the voice box or nerves to the voice box, which may cause hoarseness, shortness of breath, inability to speak • Damage to the skin, soft tissues, or other parts of the head and neck that may require a major operation to correct and, rarely, can be life threatening • Damage to the spinal cord, which may cause permanent weakness

Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

Reproductive risks: You should not get pregnant, breastfeed, or father a baby while in this study. The radiation (and chemotherapy) used in this study could be very damaging to an unborn baby. If you are a woman and become pregnant or suspect you are pregnant while participating in this study, please inform your doctor immediately.

Both men and women enrolled in this trial must agree to use adequate contraception prior to the study, while being treated on the study, and at least 60 days after finishing study treatment. Check with the study doctor about what types of birth control, or pregnancy prevention, to use while in this study.

What possible benefits can I expect from taking part in this study?

It is not possible to know at this time if the study approach is better than the usual approach, so this study may or may not help you. This study will help researchers learn things that will help people in the future.

Can I stop taking part in this study?

Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

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

The study doctor may take you out of the study:

- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the study rules
- If the study is stopped by the sponsor, IRB or FDA.

What are my rights in this study?

Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

For questions about your rights while in this study, call the _____ *(insert name of center)* Institutional Review Board at _____ *(insert telephone number). (Note to Local Investigator: Contact information for patient representatives or other individuals at a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can also be listed here.)*

What are the costs of taking part in this study? (5/17/16)

Your biopsy and the p16 testing will be reviewed by another pathologist (central review) to determine whether you are eligible to participate in this study. Your tumor may have been tested by your doctor for p16 previously, which is usually billed to your insurance, but this is not enough to qualify for the study without the confirmatory central review. You and your insurance company will not be responsible for the cost of the central review.

You and/or your health plan/insurance company will need to pay for the costs of radiation therapy and chemotherapy (for group 1) or radiation therapy alone (group 2) while in this study, including the cost of tests, procedures, or medicines to manage any side effects, unless you are told that certain tests are supplied at no charge. Before you decide to be in the study, you should check with your health plan or insurance company to find out exactly what they will pay for.

Your doctor may recommend that you have a PET/CT scan before starting treatment or during treatment. You and/or your health plan/insurance company will need to pay for the costs of the PET/CT scans, including the cost of tests, procedures, or medicines to manage any side effects. Before you have these scans, it is advised to check with your health plan or insurance company to find out exactly what they will pay for.

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

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

If you are injured or hurt as a result of taking part in this study and need medical treatment, please tell your study doctor. The study sponsors will not offer to pay for medical treatment for injury. Your insurance company may not be willing to pay for study-related injury. If you have no insurance, you would be responsible for any costs.

If you feel this injury was a result of medical error, you keep all your legal rights to receive payment for this even though you are in a study.

Who will see my medical information? (4/29/15)

Your privacy is very important to us and the researchers will make every effort to protect it. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, the researchers will do their best to make sure that any information that is released will not identify you. Some of your health information, and/or information about your specimen, from this study will be kept in a central database for research. Your name or contact information will not be put in the database.

There are organizations that may inspect your records. These organizations are required to make sure your information is kept private, unless required by law to provide information. Some of these organizations are:

- NRG Oncology
- The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study.
- The Food and Drug Administration and the National Cancer Institute in the U.S., and similar ones if other countries are involved in the study.

- VisionTree Software, Inc.

Where can I get more information?

You may visit the NCI Web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Who can answer my questions about this study?

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor _____ *(insert name of study doctor[s])* at _____ *(insert telephone number).*

THIS SECTION IS ABOUT OPTIONAL STUDIES YOU CAN CHOOSE TO TAKE PART IN

This part of the consent form is about optional studies that you can choose to take part in. You will not get health benefits from any of these studies. The researchers leading this optional study hope the results will help other people with cancer in the future.

The results will be added to your medical records and you or your study doctor will know the results.

You can still take part in the main study even if you say 'no' to any or all of these studies. If you sign up for but cannot complete any of the studies for any reason, you can still take part in the main study.

Circle your choice of "yes" or "no" for each of the following studies.

1. Optional Imaging Study – extra scan (5/17/16)

If you choose to take part in this part of the study, you will have an extra PET/CT scan a few months after treatment. This scan frequently is used in medical care for patients with your type of cancer, but it is not considered essential. Researchers would use this scan to learn more about how PET/CT scans appear in patients receiving these cancer treatments.

Compared to the targeted radiation treatments described above, the PET/CT scan radiation is at a low level and is not focused on one part of the body. This type of low level radiation is similar to "background radiation".If you have an extra PET/CT scan as part of being in this study, it will expose you to extra radiation (less than 25 mSv), which is comparable to about 8 years of natural background radiation. An average person in the U.S. receives an effective dose of about 3 mSv per year from naturally occurring radioactive materials and cosmic radiation from outer space. Most of the time, this low amount of extra radiation from the surrounding environment is not harmful to you. However, scientists believe that being exposed to too much radiation can cause harmful side effects, including causing a new cancer. For instance, for a person over the age of 60, it is estimated that a new cancer could occur in fewer than 1 of every 1000 people who receive 25 mSv.
If you choose to have this PET/CT scan after treatment, you and/or your health plan/insurance company will need to pay for the costs of the PET/CT scan , including the cost of tests, procedures, or medicines to manage

any side effects. Before you have this extra scan, it is advised to check with your health plan or insurance company to find out exactly what they will pay for.

If you agree to have the extra scan, it would involve additional radiation and placement of radioactive labeled sugar into your veins. The information from the scan may be used to guide your medical care.

Please circle your answer: I choose to take part in the imaging study and will have the extra PET/CT scan.

YES NO

2. Optional Quality of Life Study (4/29/15)

If you choose to take part in this study, you will be asked to fill out a form with questions about your communication, eating, pain, and well-being. This form is in addition to the required form about swallowing for all patients in the study. Researchers will use this information to learn more about how cancer and cancer treatment affects people.

You will be asked to fill out this form at 5 times:

- Before treatment
- After radiation therapy ends
- At 6, 12, and 24 months from the end of radiation therapy

Each form will take about 5-10 minutes to complete. The form will ask about things like your pain, activity level, speech, taste, and shoulder function. You may feel uncomfortable answering some of the questions, and you can skip any you do not want to answer.

In the past, patients often have filled out these quality of life questionnaires on paper. NRG Oncology is working with a company, VisionTree Software, Inc., that has a web site where patients can fill out these questionnaires anywhere there is a computer with Internet access. This option is being offered as some patients may find it more convenient to fill out the forms electronically from any location, including home. When you log on to the web site, it will take you through the process of completing the questionnaires step by step. You will need an e-mail address that you agree to use for this purpose. The e-mail address is needed to identify you on the VisionTree web site and for e-mail reminders that will be sent to you when the questionnaires are due. Your e-mail address will only be used for the purpose of this study, not for mail or marketing purposes. If you are interested in filling out quality of life questionnaires electronically but do not have an e-mail address, you may obtain one (quickly and for no charge at web sites such as Yahoo!, Hotmail, or AOL). You will only be sent e-mail reminders at the time that the questionnaires are due (a maximum of 3 e-mail reminders per time point). Your access to the VisionTree web site is password protected and secure. You can use your e-mail address to retrieve your password if you forget it or lose your login card. You will receive a login card either by regular mail or e-mail, and it will include the information you need to log in to the VisonTree web site the first time. All patients will complete the questionnaires before treatment on paper. After that, you can choose to complete the remaining questionnaires online or on paper. The choice is up to you.

Please circle your answer: I choose to take part in the Quality of Life study and will fill out the forms:

YES NO

Please circle your answer: I choose to use the VisionTree Software. I agree to fill out the Quality of Life Questionnaires electronically (after treatment has started) using the VisonTree web site.

YES NO

3. Optional Modified Barium Swallow (MBS) Study (5/17/16)

If you choose to take part in this study, you will have a modified barium swallow (MBS) study, a special x-ray to check your swallowing ability. During this x-ray, you will be asked to swallow small amounts of liquid and food mixed with barium. Barium is a liquid or paste that allows your mouth, throat, and swallowing tube (esophagus) to be seen on x-ray. The x-ray shows the liquid or food moving from your mouth through your throat and into your esophagus. This study allows your doctor to see if part(s) of your mouth or throat is weak, or not coordinated and if liquid or food is entering your lungs.

The radiation for this special x-ray is at a low level and is not focused on one part of the body. This type of low level radiation is similar to "background radiation" (described above). If you are a woman who is able to have children, you should inform your doctor if there is any possibility that you are pregnant. Some patients may be allergic to the barium or to flavoring added to it. If you have experienced allergic reactions after eating chocolate, certain berries, or citrus fruit, be sure to tell your doctor. If barium accidentally gets into your lungs because you choke, it does not cause any lasting harm. There is a slight chance that some barium could stay in your digestive system and lead to a blockage of the system. If you have a known obstruction in your digestive system, you should not have this x-ray.

If you choose to take part in the optional modified barium swallow (MBS) study, the tests will not be billed to your insurance. Funding for the tests has been provided by the National Cancer Institute.

Researchers will use this information to learn more about how cancer and cancer treatment affects your swallowing ability.

If you choose to take part, you will have an MBS at 2 times: Before treatment and 2 years after the end of radiation treatment.

Please circle your answer: I choose to take part in the MBS study.

YES NO

4. Optional Sample Collections for Biobanking for Possible Future Studies (5/17/16)

Researchers are trying to learn more about cancer, diabetes, and other health problems. Much of this research is done using samples from your tissue, blood, urine, or other fluids. Through these studies, researchers hope to find new ways to prevent, detect, treat, or cure health problems.

Some of these studies may be about genes. Genes carry information about features that are found in you and in people who are related to you. Researchers are interested in the way that genes affect how your body responds to treatment.

If you choose to take part, a sample of tissue from your previous biopsy and some of your blood will be collected . The researchers ask your permission to store and use your samples and related health information (for example, your response to cancer treatment, results of study tests and medicines you are given) for medical research. The research that may be done is unknown at this time. Storing samples for future studies is called "biobanking". The Biobank is being run by NRG Oncology and supported by the National Cancer Institute.

WHAT IS INVOLVED?

If you agree to take part, here is what will happen next:

1) About 2 tablespoons of blood will be collected from a vein in your arm at the same time that other blood is drawn before radiation therapy starts, at the end of 2 weeks of radiation therapy, and at 2 weeks to 1 month after you finish radiation therapy and a sample from the tissue that was collected in a prior biopsy will be sent to the Biobank.
2) Your sample and some related health information may be stored in the Biobank, along with samples and information from other people who take part. The samples will be kept until they are used up. Information from your medical record will be updated from time to time.
3) Qualified researchers can submit a request to use the materials stored in the Biobanks. A science committee at the clinical trials organization, and/or the National Cancer Institute, will review each request. There will also be an ethics review to ensure that the request is necessary and proper. Researchers will not be given your name or any other information that could directly identify you.
4) Neither you nor your study doctor will be notified when research will be conducted or given reports or other information about any research that is done using your samples.
5) Some of your genetic and health information may be placed in central databases that may be public, along with information from many other people. Information that could directly identify you will not be included.

WHAT ARE THE POSSIBLE RISKS?

1) The most common risks related to drawing blood from your arm are brief pain and possibly a bruise.
2) There is a risk that someone could get access to the personal information in your medical records or other information researchers have stored about you.
3) There can be a risk in knowing genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a research study. Even though your genes are unique, you share some of the same genes with your blood relatives. Although we are not able to know all of the risks from taking part in research on inherited traits, we believe that the risks to you and your family are very low, because your samples will be coded. Research results will not be returned to you or your doctor.

   Very rarely health or genetic information could be misused by employers, insurance companies, and others. For example, life insurance companies may charge a higher rate based on this information. Some states have laws to protect against genetic discrimination [*list appropriate state information if your state has such laws]*. A federal law called the Genetic Information Non-Discrimination Act, or GINA is in effect. This law does not allow discrimination by insurers or employers. The law does not include other types of misuse by life insurance, disability, or long term care insurance. To learn more about the GINA Law, please ask [*Note to local investigator: List contact information here for patient representatives or other individuals who take calls regarding clinical trials but who are not on the site IRB or research team.*]

HOW WILL INFORMATION ABOUT ME BE KEPT PRIVATE?

Your privacy is very important to the researchers and they will make every effort to protect it. Here are just a few of the steps they will take:

1) When your samples are sent to the researchers, no information identifying you (such as your name) will be sent. Samples will be identified by a unique code only.
2) The list that links the unique code to your name will be kept separate from your sample and health information. Any Biobank and NRG Oncology staff with access to the list must sign an agreement to keep your identity confidential.
3) Researchers to whom NRG Oncology sends your sample and information will not know who you are. They must also sign an agreement that they will not try to find out who you are.
4) Information that identifies you will not be given to anyone, unless required by law.

5) If research results are published, your name and other personal information will not be used.

WHAT ARE THE POSSIBLE BENEFITS?

You will not benefit from taking part. The researchers, using the samples from you and others, might make discoveries that could help people in the future.

ARE THERE ANY COSTS OR PAYMENTS?

There are no costs to you or your insurance for the optional biobanking for future studies. You will not be paid for taking part. If any of the research leads to new tests, drugs, or other commercial products, you will not share in any profits.

WHAT IF I CHANGE MY MIND?

If you decide you no longer want your samples to be used, you can call the study doctor, _____, *(insert name of study doctor for main trial)* at _____ *(insert telephone number of study doctor for main trial)* who will let the researchers know. Then, any sample that remains in the bank will no longer be used and related health information will no longer be collected. Samples or related information that have already been given to or used by researchers will not be returned.

WHAT IF I HAVE MORE QUESTIONS?

If you have questions about the use of your samples for research, contact the study doctor, _____, *(insert name of study doctor for main trial)*, at _____ *(insert telephone number of study doctor for main trial)*.

Please circle your answer to show whether or not you would like to take part in each option:

SAMPLES FOR FUTURE RESEARCH STUDIES:

My samples and related information may be kept in a Biobank for use in future health research.

YES NO

I agree that my study doctor, or their representative, may contact me or my physician to see if I wish to participate in other research in the future.

YES NO

This is the end of the section about optional studies.

My Signature Agreeing to Take Part in the Main Study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed copy of this form. I agree to take part in the main study and any additional studies where I circled 'yes'.

Participant's signature_____

Date of signature_____

Signature of person(s) conducting the informed consent discussion_____

Date of signature_____