NRG Oncology

Radiation Therapy Oncology Group

NRG-GU006

(ClinicalTrials.gov NCT #: 03371719)

A Phase II, Double-Blinded, Placebo-Controlled Randomized Trial of Salvage Radiotherapy With or Without Enhanced Anti-Androgen Therapy With Apalutamide in Recurrent Prostate Cancer (BALANCE*)

NRG-GU006 Consent Form

Study Title for Study Participants: Testing the addition of the drug apalutamide to radiation therapy in prostate cancer

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: NRG-GU006, A Phase II, Double-Blinded, Placebo-Controlled Randomized Trial of Salvage Radiotherapy With or Without Enhanced Anti-Androgen Therapy With Apalutamide in Recurrent Prostate Cancer (BALANCE*) (NCT# 03371719) (24-SEP-2020)

** **B**iomarker trial of **A**pa**L**utamide and r**A**diation for recurre**N**t prostate **C**anc**E**r*

What is the usual approach to my prostate cancer*?*

You are being asked to take part in this research study because you have prostate cancer and had surgery to remove your prostate. Your PSA level (a measure of prostate cancer) shows that your cancer has returned. People who are not in a study are usually treated with radiation therapy by itself. Some patients may also receive hormone suppression drugs, but these drugs are FDA approved for more advanced prostate cancer or prostate cancer that has spread. Therefore, hormone suppression drugs are usually not given unless PSA levels or other tumor factors are higher or more aggressive than yours. For patients who receive the usual approach to this cancer with radiation therapy alone, about 62 of 100 patients are free of cancer at 5 years after radiation therapy.

Some older patients with a slowly increasing PSA which means a less aggressive cancer may be candidates for observation and not receive treatment.

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
- you may choose watchful waiting and choose not to receive treatment unless symptoms appear or change
- 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? (14Jun2018)

The purpose of this study is to compare any good and bad effects of using the drug apalutamide (study drug) along with usual radiation therapy to using usual radiation therapy alone. The study drug is a hormone suppression drug. The study drug is FDA approved for the treatment of non-metastatic castration resistant prostate cancer; however, the study drug is still considered investigational in this trial setting. The addition of the study drug to usual radiation could shrink your cancer/prevent it from returning, but it could also cause side effects. This study will allow the researchers to know whether this different approach is better, the same, or

worse than the usual approach. To be better, the study drug should reduce the chance of your cancer growing back compared to the usual approach. There will be about 324 people taking part in this study.

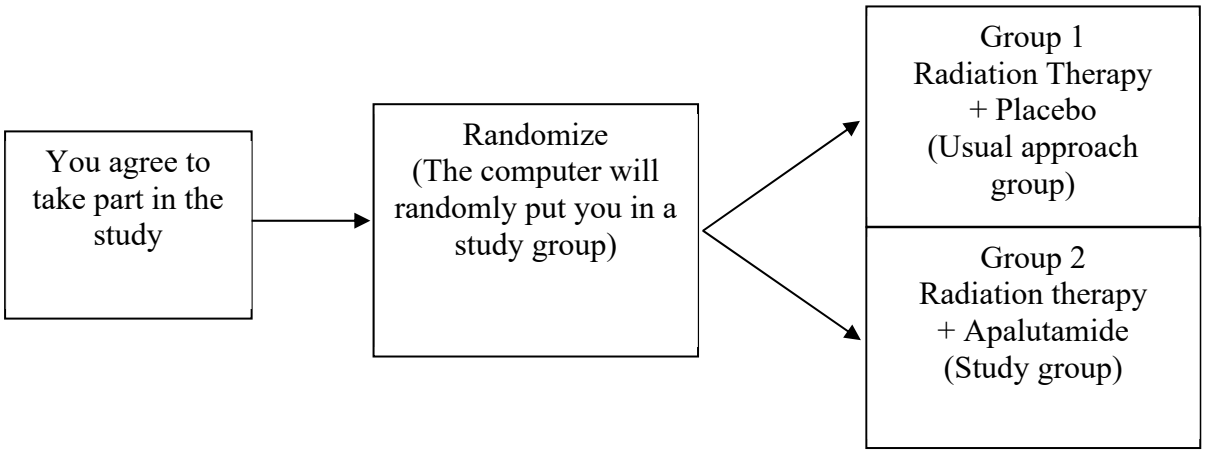
What are the study groups?

This study has two study groups.

- Group 1 will get the usual radiation therapy used for this type of cancer plus a placebo, a pill that looks like the study drug but contains no medication .
- Group 2 will get the usual radiation therapy used for this type of cancer plus the study drug.

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 others. You will have an equal chance of being placed in either group. You and your study doctor will not know whether you have been placed in Group 1 or Group 2.

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?

You will receive radiation for 7 to 8 weeks. You will start taking the study drug/placebo when you start radiation therapy, and the study drug/placebo will be taken by mouth once daily with or without food for 6 months. After you finish treatment, your doctor will continue to watch you for side effects and follow your condition every 3 months for 2 years, then every 6 months for 3 years, and then yearly via office visits.

What extra tests and procedures will I have if I take part in this study? (24-SEP-2020)

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.

<u>Before you begin treatment on the study</u>:

- Small pieces of cancer tissue removed at the time of your surgery will be taken for the study before you begin treatment on this study. This sample is required in order for you to take part in this study because the research on the sample is an important part of the study. Your study doctor will send this tissue to a

laboratory where the tissue will be tested for certain genetic markers. The results from this test will provide what is called the Decipher score and the PAM50 subtype. Your study doctor will be given a copy of the Decipher results once your protocol therapy is completed and will discuss them with you at that time if you would like to do so.You and your study doctor will not know the results of the PAM50 subtype. The results may provide useful information about your response to the treatment; however, they do not impact the treatment you will receive for your cancer during the study. If any of the tissue is left over and you choose to give your consent, it will be stored for biobanking. Biobanking will be discussed in the section on optional studies. If your doctor already sent your tumor tissue for this test and you have a Decipher risk score, the report will be submitted for review and a tissue sample will not be required.

<u>During the study</u>:

- A blood test to monitor your thyroid function will be done approximately once a month for the 6 months you receive study drug/placebo and then approximately 3 and 6 months after your last dose of the study drug/placebo.

  A blood test to monitor your organ function, electrolytes, and blood counts will be done approximately 3 months after you finish radiation therapy.

- <u>Symptoms Survey</u>
  If you speak and understand English or Spanish, you will be asked to answer questions about side effects and symptoms you may have during the study. This is part of the study that looks at how the study treatment is affecting you. You will be asked questions about side effects like diarrhea and rash. Researchers will use this information to learn more about how cancer and cancer treatment affect people, and it may help future patients understand the side effects of treatment.

  You will be asked to fill out the symptoms survey at the following times, and each time it will take about 5 to 10 minutes to complete:
  - Before you start radiation therapy
  - During the last week of radiation therapy
  - After you finish radiation therapy: every 3 months for 2 years.

  If you are having any severe symptoms, health issues or other concerns, please be sure to discuss these with your doctor or nurse.

  If you speak and understand English, you will have the option of completing the survey by paper or by an electronic device (See *Section Below). If you speak and understand Spanish but not English, you will complete the survey by paper.

  *<u>*Option for completing Symptoms Survey with a personal electronic device*</u>
  If you speak and understand English, you will have the option of completing the survey by paper or by an electronic device. If you choose to complete the survey with an electronic device, you will enter your answers to the survey via a personal electronic device such as your smart phone or tablet. This may result in minor increases in your cell phone data usage. In some cases, your clinic may provide a tablet for you to answer the survey during your clinic visits. Whether you use a personal device or a tablet supplied by the clinic, your answers and personal information will not be stored on the device. Your answers will be sent to the research database and will be kept private in the same way listed in the later section about who will see your medical records. Your e-mail address will only be used for this survey study and will not be used for mail or marketing purposes. NRG Oncology will not keep your e-mail address. All patients will complete the survey before treatment on paper. After that, you can choose to complete the remaining forms online or

on paper. The choice is up to you. If you choose to complete questionnaires using an electronic device, see Appendix I of this document for more information.

Please circle your answer:

I choose to use the electronic software for completing the Symptom Survey. I agree to fill out the Symptoms Survey forms electronically (after treatment has started).

YES NO

What possible risks can I expect from taking part in this study? (24-SEP-2020)

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

- 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
- The study approach may not be better, and could possibly be worse, than the usual approach for your cancer.
- The study approach excludes you from receiving older types of hormone therapy, which may benefit you.
- There is a risk someone could get access to the personal information in your medical records or other information researchers have kept about you. Someone might be able to trace this information back to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information. In some cases, this information could be used to make it harder for you to get or keep a job. (For non-U.S. participants, please verify the existence of such laws before including the following sentence.) There are laws against misuse of genetic information, but they may not give full protection. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.
- There can also be a risk in finding out new genetic information about you. New health information about inherited traits that might affect you or your blood relatives could be found during a study.

The radiation and drug therapy used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study approach.

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.

Study Groups 1 and Groups 2: Possible side effects of prostate bed radiation (excluding pelvis), **which is the usual approach for this type of cancer:**

COMMON, SOME MAY BE SERIOUS In 100 people receiving prostate radiation, more than 20 and up to 100 may have:
• Need to urinate more often • Urgency with urination • Slower urinary flow • Pain, including with urination and/or bowel movements • Hair loss in the treatment area, may be permanent • Tiredness • Abnormal sexual function, may be permanent

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving prostate radiation, from 4 to 20 may have:
• Chronic bowel/bladder symptoms as described above • Blood in urine • Inability to control urine, inability to control bowel movements • Diarrhea • Bleeding of the rectum • Swelling, redness, rash, skin changes, or itching in the area of radiation

RARE, AND SERIOUS In 100 people receiving prostate radiation, 3 or fewer may have:
• Blockage of internal organs that may require surgery • Damage to or bleeding of the rectum requiring surgery • A new cancer resulting from treatment of earlier cancer

Study Group 2 - In addition to side effects outlined above, people who are in Group 2 may also experience the possible side effects of apalutamide listed below.

Possible Side Effects of Apalutamide

COMMON, SOME MAY BE SERIOUS In 100 people receiving apalutamide, more than 10 and up to 100 may have:
• Fatigue • Skin rash • Joint pain or muscle spasms • Weight Loss • Fall • Fracture • Increased blood pressure • Hot Flush • Diarrhea • Decreased appetite

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving apalutamide, from 1 to 10 may have:
• Itching • High levels of fat in the blood • Changes in thyroid function. Signs and symptoms may include: extreme tiredness or changes in mood or behavior; decreased sex drive; weight gain. • Changes in taste • Decreased or blocked blood flow to the heart, heart attack • Decreased or blocked blood flow to the brain, stroke

RARE, AND SERIOUS In 100 people receiving apalutamide, fewer than 1 may have:
• Seizure

FREQUENCY UNKNOWN This is information provided voluntarily by doctors using apalutamide in routine clinical practice; not from clinical trials, from a population of uncertain size; therefore, it is not possible to estimate frequency or exclude a causal relationship to apalutamide.
• Inflammation within the lungs that may lead to permanent damage (interstitial lung disease) • Life-threatening rash with blisters and peeling over much of the body (toxic epidermal necrolysis)

Seizures have been observed very rarely in patients taking part in apalutamide studies. Your doctor will confirm that you have no history of seizures and will check throughout the study that you are not taking other medications that can increase your risk of seizures. Please inform your doctor of all medications you are taking and any changes in medications. If you think you might have had a seizure, or convulsion, or have lost consciousness (passed out), let your doctor know right away.

More than 1 in 10 patients have developed a rash. Some rashes may need medical attention. The rash may be confined to one area of your body or may spread across your body. Contact your doctor at the first sign of rash or any symptoms of rash (like itching) during the study. Rashes that are painful, blisters on or near the lips, eyes or genitals may need immediate evaluation by your doctor. You may be given medicines to apply to your skin or take by mouth to help the signs and symptoms of rash. Also, the study medication may be temporarily held.

Scarring of the inner lining of the lung (interstitial lung disease) has been observed in patients taking apalutamide. Inform your doctor if you have any history of lung problems. Contact your doctor right away if you experience symptoms such as shortness of breath, breathing difficulty, cough or fever.

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.

Additional Drug Risks
The study drug could interact with other drugs. Apalutamide may have a stronger effect or apalutamide may decrease the effectiveness of other drugs.

There are a number of drugs that are not allowed to be taken while receiving apalutamide. If you are taking this drug, your treating physician will discuss your options and the possibility of taking a different medication.

Rarely, there are problems getting enough supplies of the study drug. If that happens, your doctor will talk with you about your options.

Reproductive risks:
The effect of the study drug on your semen is unknown. To avoid risk of drug exposure to your partner through the semen (even in men with vasectomies [tubes that carry semen from the testicles have been cut]), patients must use a condom during sexual activity while on study drug and for 3 months following the last dose of study drug.

Apalutamide may cause harm to the unborn child. From when you start taking the study drug until 3 months after your last dose of study drug, you must use a condom and another effective method of birth control when you have sex with a woman of child-bearing potential. The type of birth control you use must be discussed with, and approved by, the study doctor before you begin the study. This is done to prevent pregnancy. If your partner becomes pregnant in the time between when you start taking the study drug until 3 months after your last dose of drug, you must tell the study doctor immediately.

Donation of sperm is not allowed during the study and for 3 months following the last dose of study drug.

You should advise your study doctor if you father a child while participating in the research project. The doctor will advise you on any appropriate medical attention for your partner should this be necessary. The sponsor may ask you and your partner to allow him/her to collect information about her pregnancy and the health of the baby.

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?

The study drug or placebo will be supplied by Janssen at no charge while you take part in this study. The cost of getting the study drug or placebo ready and giving it to you is not paid by the study sponsor so you or your insurance company may have to pay for this. It is possible that the study drug/placebo may not continue to be supplied while you are on the study. Although not likely, if this occurs, your study doctor will talk to you about your options.

You and/or your health plan/insurance company will need to pay for all of the other costs of treating your cancer 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.

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? (15-JUL-2019)

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
- Janssen, the drug company supporting the study
- 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.
- The NCI's National Clinical Trials Network and the groups it works with to conduct research, including the Imaging and Radiation Oncology Core (IROC) and the the Cancer Trials Support Unit (CTSU).
- GenomeDx Biosciences

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).*

ADDITIONAL STUDIES SECTION:(15-JUL-2019)

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 not be added to your medical records and you or your study doctor will not know the results.

You will not be billed for these optional studies. 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 Sample Collections for Laboratory Studies and/or Biobanking for Possible Future Studies

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.

Blood Laboratory Study for Circulating Tumor Cell Analysis.
If you choose to take part in this study, the study doctor for the main study would like to collect blood for research on cancer cells that may be in your bloodstream. These circulating tumor cells (CTCs) may give the study doctors additional information about your cancer. They would like to see if it is possible to get the same information from your blood that they can get from the molecular test of your prostate tissue. Research results will not be returned to you or your doctor

Blood Laboratory Study for Genetic Changes
If you choose to take part in this study, the study doctor for the main study would like to collect blood for research on genetic changes in your blood that may give the study doctors additional information about your cancer.

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. See *What Are the Possible Risks* below for further details.

Specimen Banking for Future Research

If you choose to take part, blood, urine, and a sample of tissue from your previous biopsy will be collected. Only researchers authorized will have access to your banked samples. 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? (15-JUL-2019)

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

Laboratory Studies

1) About 3 tablespoons of blood will be collected from a vein in your arm at the following times that you have blood taken as part of your participation on the main part of the study: before you begin treatment, at the end of treatment, and if your tumor comes back.
2) Your sample and some related health information will be sent to a researcher for use in the studies described above. Remaining samples may be stored in the Biobank, along with samples from other people who take part. The samples will be kept until they are used up.

Banking for Future Research

3) A sample from the tissue that was collected at the time of your surgery will be sent to the Biobank.
4) About 3 tablespoons of blood will be collected from a vein in your arm at the following times that you have blood taken as part of your participation on the main part of the study: before you begin treatment, at the end of treatment, and if your tumor comes back
5) A sample of urine your urine will be collected before you begin study drug/placebo treatment at the same time that you visit your doctor as part of your participation on the main part of the study.

The following apply to both studies

6) 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.
7) 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.
8) 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.
9) 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 is a risk that someone could trace the information in a central database back to you. Even without your name or other identifiers, your genetic information is unique to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.
4) 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; for non-US participants, please verify existence of such laws before including the following text]*. 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 sample(s) is 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 you 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. 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? (15-JUL-2019)

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 THE LABORATORY STUDIES:

I agree to have my specimen collected and I agree that my specimen samples and related information may be used for the laboratory studies described above.

YES NO

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_____

(The following signature and date lines for the person(s) conducting the discussion may be included at the discretion of the study sponsor.)

Signature of person(s) conducting the informed consent discussion_____

Date of signature_____

Appendix I: Patient Instructions for Accessing the Patient Cloud Using Your Personal Device

Downloading the Patient Cloud ePRO App

If you are using your personal device, and you do not have the Patient Cloud ePRO app, use the following instructions. When downloading the app, you must use the Apple ID or Google account associated with the device. If the Patient Cloud ePRO app is already on the device, or if you are using a provider's device, you can skip this section.

You will need an email address that you agree to use for this purpose. The e-mail address is needed to identify you on the Patient Cloud Application and for you to receive notifications to let you know when forms are due. Your e-mail address will only be used for this survey study, and will not be used for mail or marketing purposes.

If you decide to use the electronic method to complete the questionnaires, and do not have an e-mail address, you may sign up for one at no charge at many different websites. A few sites that are commonly used and will allow you to create an email address very easily are Yahoo, Gmail, and Outlook.

For iOS:

1. An Apple ID is required for downloading the Patient Cloud ePRO app.
2. Tap the *App Store* icon.
3. Search for *Medidata Patient Cloud* and follow the installation instructions.

Note: Patient Cloud ePRO is listed as an iPhone App in the App store. When using an iPad, please view the search results under iPhone apps.

For Android:

1. A Google account is required for downloading the Patient Cloud ePRO app
2. Tap the *Play Store* icon.
3. Search for *Medidata Patient Cloud* and follow the installation instructions.

Registering

You must register in order to complete and submit your study forms. When you register, you will create a username, which is your email address, and a password that allows you to log in to the Patient Cloud ePRO app.

Note**:** You must have an activation code to begin this process. If you do not have an activation code, please contact your provider.

There are two possible ways to register. Your provider may have sent you a link to a web address where you may register from any web browser, including the one on your device. The other way to register is on the Patient Cloud ePRO app.

1. If registering from the Patient Cloud app, tap Register on the bottom of the log in page. If registering on the web, open the URL shield.imedidata.com on a web browser.
2. Enter your activation code and tap Activate.
3. On the next page, read the instructions and tap Next.
4. Read the privacy notice and tap I agree. Then tap OK to confirm.
5. Enter and confirm your email address. Tap Next.

6. Enter and confirm your password. Tap Next.
7. Choose a security question by scrolling through the dropdown menu to display the question of your choice.
8. Enter your security question response.
9. Tap Create my account to complete your registration.

If you registered on the Patient Cloud ePRO app, it automatically logs you out. If you registered on the web, you are presented with the option to download the Patient Cloud ePRO app. You can then proceed to log in with the credentials you created.

Logging in to the App

1. Enter your Email and Password that you created during the registration process. (If you previously set a PIN code, just enter your four-digit PIN.)
2. Tap Log in.

Note: If you do not remember your password, tap **Forgot Password**, and follow the instructions provided.

Setting a PIN Code

The first time you log in to the Patient Cloud ePRO app, you are given the option to create a PIN code. A PIN code allows you to bypass the step of entering your email and password every time you need to log in to the Patient Cloud ePRO app. Instead, you can enter a four-digit PIN.

1. If you wish to set a PIN code the first time you log in, tap Yes when prompted.
2. Note: You can also set your PIN at a later time by tapping the options menu on the top left of most pages and selecting Set PIN.
3. Enter a four-digit PIN.
4. Re-enter the four-digit PIN to confirm.

If you forget your PIN code, tap **Forgot PIN** and you can access the app using your email and password. You may reset your PIN by tapping the options menu on the top left of most pages and selecting Set PIN.

Resetting Your Password

You can reset your password by using the options menu at the top left of most pages.

1. Tap the options menu icon.
2. Tap Reset Password.
3. Follow the instructions to reset your password.

Completing and Submitting Forms

Once logged in, forms related to your study display on the Tasks page. If you are enrolled in multiple studies, select the appropriate study first, and then select a form. New forms can appear on the Tasks page at any time, depending on how the study is designed.

There are two types of forms displayed on the Task List page:

- *Scheduled Forms* (with a  icon): These forms have a "Due Date" indicator in them so you are aware of the last day by which you will need to complete the form. If the form is due in less than one day, you will see the due time in hours.
- *Anytime Forms* (with a  icon): These forms have "Last Completed Time" indicator on them which tells the most recent date or time when you completed the form. If you start a form, but do not complete it, you will see an 'Incomplete" status beneath the form name, along with a half-moon icon.

1. Select the appropriate form.
2. Follow the on-screen instructions until you reach the end of the form where you are given the opportunity to review and change your responses prior to submitting.
3. Review your responses by scrolling down the list.
4. If you need to change an answer, tap the question to go back and change the answer.
5. When you are ready to submit, tap Submit Your Data.

Note: Once a form is submitted, you will be unable to edit any of your responses. In some cases, you may be asked to acknowledge your submission by entering your password.