The Children's Hospital of Philadelphia®

Informed Consent Form and HIPAA Authorization

Study Title: **Phase 2 Study of Humanized CD19-directed Chimeric Antigen Receptor-modified T Cells (huCART19) for Very High-Risk Subsets of B cell Acute Lymphoblastic Leukemia (B-ALL)**

Version Date: **February 2, 2022**

Principal Investigator: Shannon Maude, MD, PhD [redacted]

Affiliation: The Children's Hospital of Philadelphia, Division of Oncology

Emergency Contact: Shannon Maude, MD, PhD [redacted]

Sponsor: University of Pennsylvania

You, or your child, may be eligible to take part in a research study. This form gives you important information about the study. It describes the purpose of this research study, and the risks and possible benefits of participating.

If there is anything in this form you do not understand, please ask questions. Please take your time. You do not have to take part in this study if you do not want to. If you take part, you can leave the study at any time.

In the sections that follow, the word "we" means the study doctor and other research staff. If you are a parent or legal guardian who is giving permission for a child, please note that the word "you" refers to your child.

Why are you being asked to take part in this study?

You are being asked to participate in this research study because your leukemia has a high risk of returning after previous treatment or you have no available curative treatment options for your leukemia.

What is the purpose of this research study?

The purpose of this study is to test an experimental approach called cell therapy for leukemia that involves B cells (your tumor cells). This is a study for people who have been treated for leukemia without good response or those whose leukemia has returned. If you have previously received a similar cell therapy, you may still be eligible for this study. This study will take your own white blood cells (T cells) and change them to turn against the cancer.

Your T cells will be changed in a way that will allow the cells to identify and kill your tumor cells. This change tells your T cells to go to the tumor cells and turn "on" and potentially kill the tumor cells. The modification is done by gene transfer and results in a genetic change to your T cells. This allows the changed T cells to recognize tumor cells and normal antibody-producing cells called B cells, but not other normal cells in your body. These changed cells are called huCART19 T cells.

These cells are an experimental kind of treatment and have not been approved by the FDA. This kind of treatment has been tested in a number of different clinical trials, and similar kinds of cells have been given to patients at both PENN and CHOP, many of whom had decreases in their disease or entered a complete remission.

How many people will take part?

We expect to enroll a total of up to 116 subjects on this study between two groups called Cohort A and Cohort B. Cohort A will enroll up to 62 subjects, and Cohort B will enroll up to 54 subjects. All subjects will be recruited from CHOP.

What is involved in the study?

How long will you be in this study?

If you agree to take part, your participation in this study will last approximately 12 months. You will be asked to spend the first 21 days after you have received huCART19 cells in close proximity to the trial treatment center. You will be followed closely for the first month after receiving huCART19 T-cells, and then monthly for 6 months, and then every 3 months for up to 12 months.

If you receive the huCART19 T cells, you will be offered enrollment in a long-term safety follow-up study after completing this study to monitor your health for up to 15 years. You will sign a separate informed consent for the long-term follow-up study. You do not have to participate in the long-term safety follow-up study in order to participate in the current study.

What are the study procedures?

If you take part in this study you will have the following tests and procedures. Some of these tests and procedures are part of taking care of a patient with cancer (regular or standard care) and assessing both the amount of disease present as well as response to any treatment, while some of these tests and procedures are related to the research.

Some of the procedures may be repeated several times. Tests that are part of your regular, routine medical care will continue to be performed. Additional tests may be performed if any of your initial test results are not normal.

Tests/procedures that are or may be done, if clinically indicated, as part of your **regular / standard clinical care**:

Medical History Review: You will be asked questions about your medical history, along with a listing of any medications you are taking.

Physical Exam: Exams will be conducted before and during the study including measurements of weight, height, and vital sign assessments, which may

include blood pressure, body temperature, respiration rate, heart rate, and oxygen saturation via pulse oximetry as clinically indicated.

Blood Tests: (approximately 1-5 tablespoons, depending on the specific visit) for routine lab tests to check the status of your health, such as complete blood counts (CBCs) and other blood tests

Bone Marrow Aspirate and Biopsy: A bone marrow aspiration is a procedure in which an area of the hipbone is numbed, and a small sample of bone marrow is removed through a needle. A bone marrow biopsy is similar to a bone marrow aspiration, except a sample of bone is removed through the needle.

Spinal Tap: Patients with ALL will have spinal fluid collected for disease testing. A needle is introduced between the backbones and a small amount of the spinal fluid is removed.

Disease Assessment: Depending on your kind and location of your tumor, you may be asked to have a lymph node biopsy (take a small piece of the lymph node with a needle) to determine your disease status.

Imaging: Depending on the kind and location of your tumor, you may be asked to have imaging tests such as a CT scan, PET scan or chest x-ray. If central nervous system (CNS) symptoms are present at Screening/Enrollment, then a lumbar puncture and brain imaging by MRI/CT will be performed to assess if the cancer has spread to your central nervous system (CNS).

Pregnancy Test: If you are a woman able to have children, a serum (blood) or urine pregnancy test will be performed. The results will be shared with you and not with your parent(s). We strongly encourage you to share the results with your parents. If you are pregnant, you will not be able to take part in this study.

Leukapheresis: In order to collect your T cells, we use a procedure called leukapheresis. If there are T cells that were previously collected from you for clinical reasons or another research study, we would like to use them for this study, if possible. The leukapheresis procedure is necessary in order to collect your white blood cells and then remove and modify (change) your T cells. In order to do the leukapheresis procedure, it may be necessary to put in a temporary catheter (central intravenous line) to collect the cells in smaller patients, while teenagers may just need two IVs. The risks of central line placement and leukapheresis are described below.

Chemotherapy: You may be treated with chemotherapy that will help your body to accept the huCART19 T cells and may also be used to decrease the amount of tumor in your body. Your doctor will decide what kind of chemotherapy you will be given depending on what chemotherapy you have received in the past and your disease type. Your doctor will discuss the side effects of any chemotherapy that you are given.

Heart Assessment: You will have an ECHO or similar test performed within 8 weeks of the first infusion.

Respiratory Assessment: A breathing test may be done to see how well your lungs are functioning.

Influenza Test: You will also undergo a rapid influenza (flu) test (only during the months of October through May) within 10 days prior to your planned huCART19 T cells. If results show you are positive for the flu, your study doctor will treat you with Tamiflu or a similar anti-flu drug in that situation.

Tests/procedures required for research purposes:

If you agree to participate in this study, you will have exams and tests done to make sure that you are eligible to take part in the study. These screening procedures will be done prior to growing the T cells. For example, some of the tests will assess organ function and determine whether your T cells are healthy enough to undergo the procedure.

Some of the screening procedures may be done as part of your usual medical care, even if you do not join the study. We may use the results to see if you are eligible for the study, instead of repeating the procedures.

We may use leftover portions of blood, bone marrow, lymph node biopsy or spinal fluid drawn as part of clinical tests for screening and research purposes if you are eligible and choose to participate in the study.

If the screening exams and tests show that you are not eligible for the study, you will not be able to continue participating in the study. If the screening exams and tests show that you qualify for the study, we will proceed with making the T cells. The study staff will discuss the eligibility criteria and the results of your screening procedures with you in more detail during the screening period.

Your T cells will be modified (changed) by gene transfer to make them recognize your tumor cells. This process takes at least 4 weeks to complete. Your modified T cells become the "study drug", which you will receive. At the end of making the T cells, we do tests to make sure the T cells grew well and are safe to give to you. If these tests do not show a safe or adequate product, we would not be able to give it. If there is a significant change in your health between screening and when we give the cells, you may not be able to receive the cell infusion or it may be delayed to allow time for recovery. You will be told when to return to the hospital to receive your study drug (huCART19 T cells).

Pre-Infusion: Approximately one day before you receive the dose of huCART19 T cells you will have a pre-infusion study visit which will consist of a physical examination including measurements of blood pressure, heart rate, respiratory rate and temperature. You will have approximately 2 tablespoons of blood drawn for routine laboratory tests, including a pregnancy test (if applicable).

huCART19 Infusion: Approximately one day later you will be asked to return to receive infusion of the study drug (huCART19 T cells), which will usually occur in Oncology clinic, but may happen in the hospital.

You will receive your huCART19 T cells either through a peripheral IV or through a central line. In order to reduce potential side effects of the huCART19 T cell infusions, you may receive acetaminophen (also known as Tylenol) and an antihistamine (such as Benadryl) (as part of clinical care). The study drug will take just a minute or 2 to infuse (go into your vein). A blood sample will be taken to measure the starting levels of huCART19 cells in your blood. It will be necessary for you to remain in the clinic for at least one hour after each infusion is completed. If you do not experience any uncomfortable effects from the infusion you will be able to leave the hospital.

The infusion may be repeated on day 14 or after. For patients who have a short response or partial response to the initial infusion, it may be that the initial dose of cells was not adequate for long-term effect. In these cases, it may be appropriate to give another infusion or infusions.

Study Follow-up Visits: You will be asked to return to the clinic twice a week for three weeks following infusion, and then once a month for up to 6 months for study visits. Monthly visits may be performed by your primary oncologist, but quarterly visits will be performed at CHOP. These visits will take about an hour and will include a routine physical exam and medical history. In addition you will have approximately 8 teaspoons (40 cc) of your blood drawn for standard laboratory tests as well as tests related to the study treatment. You will be asked to sign a permission form (release of medical information form) so that we may request medical records from your primary oncologist.

All patients will be asked to come back quarterly for 1 year for routine and study-related blood tests (up to 6 teaspoons (30cc) of blood will be taken from your arm), a physical examination, and to have a medical history taken by the study team. In addition, you will have a disease assessment every 3 months. The routine blood tests are for your regular care, and study blood tests are done to look for any side effects and to see how your body has responded to the huCART19 T cells, and to determine if they are still present in your blood.

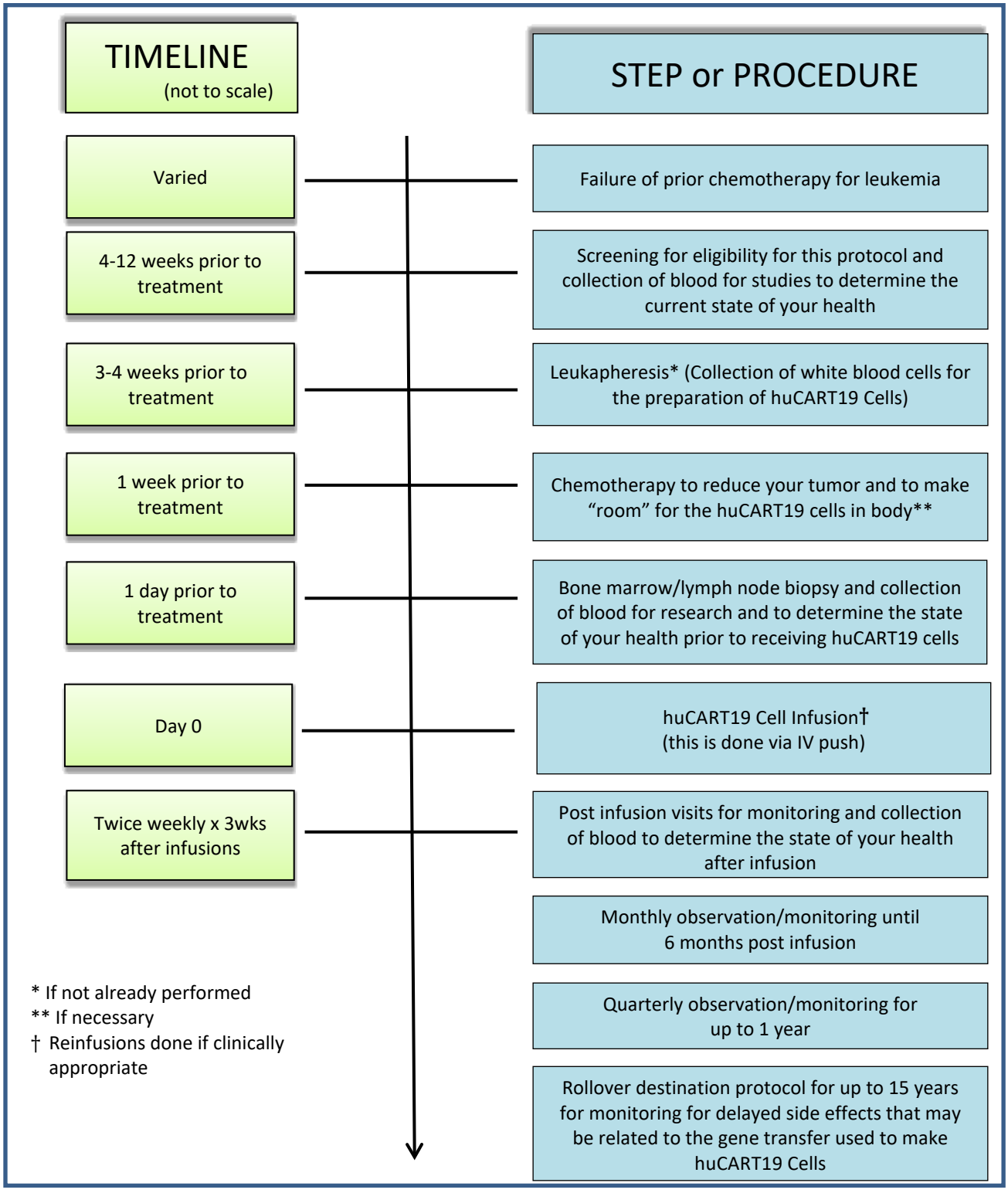
If you cannot return to the study site for follow-up visits, your primary care physician and/or local oncologist will be asked to provide information to the study team for study visits (including the results of any routine care examinations and/or laboratory assessments). We will request blood samples (if applicable) which will be sent to the University of Pennsylvania. You will be asked to sign a permission form (release of medical information form) so that we may request medical records from your primary oncologist/ primary care physician.

If re-infusions are performed, you will be asked to come back for follow-up visits after those study treatments as well. If the re-infusion study visits are scheduled at the same time as the original infusion follow-up visit, the tests/procedures will not be done more than once for that visit. You will be asked to complete all original infusion follow-up visits after the re-infusion visits are completed. Additional follow-up visits after any reinfusion may also be performed if the physician-investigator determines they are needed. If reinfusions are received, this may also further extend your follow-up and overall study participation.

Medical Record Review: We will review your medical records throughout the study to collect information about your medical history, current health, diagnoses, treatments, medications, and results of clinical tests.

Genetic Testing: Genetic testing may be done on your research samples including blood, bone marrow, and tissue samples. You will not receive the results of these tests.

A figure of the study timeline (green) and the steps and procedures this clinical protocol entails (blue) is shown below.


TIMELINE
(not to scale)
STEP or PROCEDURE
Varied
Failure of prior chemotherapy for leukemia
4-12 weeks prior to treatment
Screening for eligibility for this protocol and collection of blood for studies to determine the current state of your health
3-4 weeks prior to treatment
Leukapheresis* (Collection of white blood cells for the preparation of huCART19 Cells)
1 week prior to treatment
Chemotherapy to reduce your tumor and to make "room" for the huCART19 cells in body**
1 day prior to treatment
Bone marrow/lymph node biopsy and collection of blood for research and to determine the state of your health prior to receiving huCART19 cells
Day 0
huCART19 Cell Infusion†
(this is done via IV push)
Twice weekly x 3wks after infusions
Post infusion visits for monitoring and collection of blood to determine the state of your health after infusion
Monthly observation/monitoring until 6 months post infusion
Quarterly observation/monitoring for up to 1 year
Rollover destination protocol for up to 15 years for monitoring for delayed side effects that may be related to the gene transfer used to make huCART19 Cells
* If not already performed
** If necessary
† Reinfusions done if clinically appropriate

What are the risks of this study?

Taking part in a research study involves risks and inconveniences. You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects may be temporary. In some cases, side effects can be serious, long lasting, may never go away, or possibly result in death. If you have any questions about any of the possible risks listed below, you should talk to your study doctor or your regular doctor.

The list of side effects below contains the most common side effects of huCART19. Please notify your doctor if you experience any of the described side effects. In addition, this research may involve risks that are currently not known, so tell your doctor if you are experiencing any problems. If you see a doctor other than your study doctor, please let them know that you are involved in a research study.

It is very important that you contact your study doctor immediately at any sign of fever or other new abnormal symptoms.

While in this study, you are at risk for the following side effects:

Risks related to leukapheresis (collecting the cells that we will use to make the huCART19 modified T cells) – *These risks are part of your clinical care and are not risks of the study*

The leukapheresis procedure is usually safe, and will take several hours on one day. Side effects that can occur during T cell collection include nausea, vomiting, fainting or dizziness, seizures, skin rash, hives, flushing (redness and warmness of the skin, usually the face), blood loss, and infection. Tingling of the lips, muscle cramping and, very rarely, changes in the heart rhythm can occur. These can be prevented or made milder by giving calcium supplements, either by mouth or IV. Very rarely, (less than 1 in 1,000 procedures), clotting may occur in the leukapheresis machine or in a patient and is potentially life-threatening. To reduce the risk of clotting, you will be given a drug called ACD (acid-citrate-dextrose). This drug may increase the risk of bleeding and may cause temporary tingling of the lips and limbs, muscle cramping, seizures, or changes in the heart rhythm.

It may be necessary to place a temporary central line called a leukapheresis catheter if you don't already have an appropriate catheter. There is a risk that the temporary catheter may not function properly or get blocked during the pheresis procedure. The risks associated with central lines will be explained to you by your surgeon or radiologist and include bleeding, infection, or air within the chest. You will be given a separate informed consent form to read and sign prior to having a central line inserted. The central line procedure may require sedation or general anesthesia, and the risks will be explained to you by the doctor performing the sedation or general anesthesia. Depending on the type of sedation or anesthesia required, there may be one or more of the following side effects: nausea, vomiting, allergic reaction, air passage obstruction, breathing problems, heart irregularity, increases or decreases in blood pressure, rare reactions to medications used in the anesthesia, nerve injury, lung injury, heart attack and brain damage. An extremely rare but serious complication is rapid increase in body temperature. Note that all of these complications are treatable but might lead to coma or even death.

Potential risks related to the infusion of huCART19 modified T cells:

Very Common (occurring in > 10% of patients)

- Cytokine Release Syndrome. When the huCART19 cells grow rapidly and become activated, they can release proteins called cytokines. Release of large amounts of certain cytokines can cause a "cytokine release syndrome" that can result in mild, moderate or severe reactions. Symptoms and problems can include:
    - High fevers, fever with decreased white blood cell numbers
    - Chills and shaking
    - Fatigue
    - Decreased appetite, Nausea and vomiting
    - Headache
    - Muscle and joint aches
    - Diarrhea or constipation
    - Fast heart rate
    - Generalized pain, pain in extremities, abdominal pain, back pain
    - Decreased blood pressure
    - Decreased oxygen in your blood
    - Blood clotting can be abnormal, which has rarely resulted in bleeding.
    - Sweating
    - Swelling
    - Skin rashes, itchiness
    - Changes in blood chemistries that may require supplements (low sodium, low calcium, low potassium or low phosphate)

  Some patients have become quite ill, with breathing difficulties and low blood pressure that can be life-threatening. Some patients have required use of a respirator (a breathing machine) and medications to keep blood pressure up. This cytokine release syndrome can lead to kidney and liver problems that can be severe, and several adult patients have required at least temporary dialysis. Cytokine release syndrome can be mild or severe and can lead to death. Some patients required intensive care at the hospital for several days and some adult patients have died. Fortunately, these side effects have gotten better with medicines that block these cytokines (like tocilizumab) and/or steroid treatment. In one subject the steroid treatment kept the T cells from working. In many other subjects, tocilizumab reversed the side effects rapidly and the T cells still worked and treated the leukemia. Sometimes more than one dose of cytokine-blocking medicine is required.

- Low white blood cell numbers (the body's immune cells that protect you from infections). Anemia (low red blood cells), low platelets (cells needed for blood clotting) and low blood counts can be a side effect of the chemotherapy, of the leukemia, or of the huCART19 cells themselves, and can sometimes last for weeks. This can cause fatigue, bleeding or a skin rash and put you at risk for infection.
- Significant decrease in your B cell counts (type of white cell). Your B cell count may already be low following treatments (chemotherapy) you have previously received for your cancer, since your tumor is comprised of B cells. Likewise, a decrease in your tumor B cell counts is the goal of this study and we expect the B cell counts that you have upon enrollment into this trial to decrease (often to none) after you receive the huCART19 cells. This decrease in B cells may continue for the period of time in which your body contains the huCART19 cells, which may be months or longer. The huCART19 cells cannot distinguish between your healthy and tumor B cells.
- Bloody nose
- Upper respiratory infection, cough, nasal congestion, runny nose due to seasonal allergies
- Shortly following huCART19 infusion (days to ~2 weeks), you may experience changes in your thinking and alertness (any of altered mental status or confusion, hallucinations, delirium, weakness, unsteady balance, abnormal speech, seizures). These symptoms in children and young adults with leukemia have typically resolved within several days. In rare cases, bleeding and swelling in the brain, as well as inflammation in the spinal cord leading to loss of movement (paralysis), have also been seen.

Common (occurring in between 1 and 10% of people)

- Blurred vision
- Dizziness
- Increased blood pressure
- Acute kidney injury
- Dehydration
- Seizure
- Sensitivity to light or eye discomfort
- Infusion reactions
- Irritability
- Weight loss
- Mouth sores or pain
- Altered taste

- Runny nose, sore throat, flu like symptoms
- Shortness of breath, fluid in lungs, rapid breathing
- Heartburn, Inflammation of small intestine and the colon, incontinent of stool, GERD,
- Increase in blood chemistries (calcium, potassium, phosphorous and sodium)
- Agitation, anxiety
- Pain– this can be in joints, bones, back
- Inflammation of the pancreas which can cause abdominal pain.
- Swelling of face and limbs
- Night sweats
- If your B cell numbers decrease over time, there could be a risk of increased viral or bacterial infection because you have a decrease in the type of cells that fight these types of infections. Your doctor will be able to treat you with medications such as intravenous immunoglobulin (IVIG) which will reduce your chances of infection due to a lack of B cells. The decrease in these types of cells that fight infections minimizes the ability of your immune system and IVIG helps maintain your body's antibody levels to resist infection.
- Allergic reaction

Less Common (occurring in less than 1% of people)

- Severe breathing difficulties, including swelling of the airway
- Allergic reaction (itching, swelling of the tongue)
- Tumor Lysis Syndrome: If your tumor B cells decrease quickly, you may experience Tumor Lysis Syndrome. This happens when the leukemia cells in your body are killed quickly and the body doesn't have enough time to get rid of the dead cells. This can cause kidney damage.
- If your T cells grow rapidly it is possible that the number of huCART19 cells will significantly increase in your body. This can be a good thing. However, it is possible that the growth of the huCART19 cells will be excessive, in which case your doctor may wish to kill the huCART19 cells. This can be done by giving drugs called corticosteroids. If the huCART19 cell growth is not controlled by the corticosteroid treatment, your doctor will recommend chemotherapy, similar to what is usually administered for your B cell tumor. The main risk of short-term corticosteroids is an increased risk of infections.

You may be less likely to respond to similar gene transfer trials in the future because you may develop an immune response to the viral vector used for the gene transfer in your cells.

Other potential risks related to huCART19 modified T cells

The study involves giving you some cells that have been changed by a lentiviral vector. A lentiviral vector is a virus that can insert genetic material into cells. We use a vector to put huCART19 into

your T cells. We will not give you the vector. The vector comes from the human immunodeficiency virus (HIV, a type of virus called "lentivirus"), which causes HIV infection in humans that can lead to the acquired immunodeficiency syndrome (AIDS). The vector we use has been changed a lot so that it can't grow by itself or cause disease.

Risk of blood cancer:

When lentiviral vectors enter a normal cell in the body, the deoxyribonucleic acid (DNA) of the vector inserts itself into the normal DNA in that cell. This process is called DNA integration. Most DNA integration is expected to cause no harm to the cell or to the patient. However, there is a chance that DNA integration might result in abnormal activity of other genes. In most cases this effect will have no health consequences.

We do not know if the lentiviral vector used in this protocol might cause a new cancer. However, you should be aware that the DNA contained in these vectors will integrate into your DNA and that under some circumstances, this has been known to cause cancer months to years later.

It is important that you know about some cancers that occurred in another gene transfer research study, using a different kind of vector. The study, conducted in France, involved a disease called X-linked Severe Combined Immunodeficiency (SCID). Years after receiving cells that were modified by a vector, a significant number of the children in this small study developed cancer (like leukemia). At least one child died from the cancer. Experts who studied the children's blood cells concluded that the leukemia-like cancer was caused by the vector. However, most of the children with X-linked SCID who have received experimental gene transfer have not been found to have a leukemia-like disease, at least at this time.

Risk of a Replication Competent Lentivirus or "RCL":

There is a risk that the vector could change (mutate) and grow. If it does, it would be called a "replication competent lentivirus (RCL)". Blood samples will be collected and stored at pre-infusion and post-infusion at Months 3, 6, and 12. These samples may be used for future RCL testing if needed.

Risks Associated with HIV:

The lentiviral vector is not made with the whole HIV but only parts of HIV. It is impossible for the study vector to give you HIV. However, the cells could cause you to test positive on some types of HIV tests. This means that after you get the cells, a routine HIV test may say you have HIV, even if you don't. For this reason, you should plan to get HIV tests only at this clinic during the study. The test we use does not have this issue.

If you receive a positive test result caused by the cells at any time, we will do more HIV testing. If this happens, we do not know how long you will stay positive due to the cells. If you receive a positive HIV test result and we determine it is because you have HIV, we will refer you for care.

Risks of antibody formation:

While making the cells, we will use proteins that are foreign to your body. Strict tests are in place to make sure that foreign proteins are completely removed but it is possible that some protein could remain on the cells. Your body could develop immune responses against the cells that are given to you. This would almost certainly result in the cells disappearing from the body. This could cause

itching and swelling. In severe cases, your breathing or blood pressure could be severely affected. Doctors would treat you for these problems.

Risk of autoimmune disease:

The use of huCART19 T cells could potentially result in an illness which doctors call "autoimmune disease". Our bodies have an immune system that protects us from disease and infection. When you have an autoimmune disease, your immune system attacks itself by mistake, and you can get sick. Autoimmune diseases can affect the tissues that bind together body tissues and organs.

Autoimmune disease can affect many parts of your body, like your nerves, muscles, the endocrine system (system that directs your body's hormones and other chemicals), digestive system and others.

Risks related to Unsuccessful Manufacturing of your huCART19 modified T cells:

Unsuccessful manufacturing of your huCART19 cells: It is important to understand that meeting study eligibility does not guarantee that you will receive your huCART19 cells. It is possible that during the manufacturing, your T cells may become infected or not grow properly. If this happens you will not be able to receive your huCART19 treatment.

Reproductive risks:

It is unknown what effect(s) the huCART19 cells may have on an unborn child. As the study drug can affect a developing fetus (unborn baby in the womb), you should not become pregnant or father a baby while on this study.

For this reason, if you are of childbearing age, you will be asked to practice an effective method of birth control while participating on this study. Ask about counseling and more information about preventing pregnancy.

For Females:

The huCART19 cells given during this study can affect an unborn child. You should not become pregnant or breastfeed your baby while being treated on this study. If you are sexually active and are at risk of getting pregnant, you and your male partner(s) must use an effective method to avoid pregnancy (contraception) or you must not have sex. The study doctor will talk to you about acceptable methods to avoid pregnancy while you are being treated on this study. You will have to use the chosen method to avoid pregnancy or abstain (not have sexual intercourse) the whole time you are being treated on this study. You must continue this for at least 12 months after your cell infusions are done. Natural family planning and the rhythm method will not be permissible means of avoiding pregnancy during study participation. If you have questions about this or want to change your method to avoid pregnancy during the study, please ask your doctor. If you become pregnant during the research study, please tell the investigator and your doctor immediately.

If you are nursing a baby, there is no reason to believe that the huCART19 cells used in this research could pass into the breast milk. Nevertheless, you should not nurse your baby for the whole time you are getting the study medicines. You may need to continue this for a while, even after your cell infusions are done, so talk to your doctor about the length of time you need to avoid nursing.

For Males:

The huCART19 cells given during this study could damage sperm. You should not father a child while on this study as the huCART19 cells may indirectly affect an unborn child. If you are sexually active and are at risk of causing a pregnancy, you and your female partner(s) must use a method to avoid pregnancy (contraception) that works well or you must not have sex. The investigator will talk to you about the acceptable methods to avoid pregnancy while you are on this study. You will have to use the chosen method to avoid pregnancy or not have sex the whole time you are on this study. You must continue this for at least 12 months after your cell infusions are done. Natural family planning and the rhythm method will not be acceptable ways of avoiding pregnancy during study participation. If you have questions about this or want to change your method to avoid pregnancy during the study, please ask your doctor. If your partner becomes pregnant during the research study, please tell the investigator and your doctor immediately. Your pregnant partner will be asked to sign an additional consent form in order for the study team to follow the outcome of your partner's pregnancy and the health of the baby.

Medically acceptable birth control includes at least one of the following methods:

- Condoms (male or female) with or without a spermicidal agent
- Diaphragm or cervical cap with spermicide
- Intrauterine device (IUD)
- Hormonal-based contraception

Treatment on this study may have risks we don't know about.

We may stop this treatment if we learn of serious, unexpected risks. We will explain the effects of stopping, and we will offer other treatments.

Additional Risks:

Graft-vs-host disease (applies only to patients who have had a bone marrow transplant):

You are familiar with the risk of graft-vs-host disease (GVHD), which was a major anticipated side effect of your original transplant. Whenever additional donor T cells are given to a patient as "donor lymphocyte infusions", they can cause GVHD. Approximately 40-50% of patients who get a similar dose of unmodified T cells from their donor (donor T cells or white blood cells that do not have any gene put in them to target CD19) develop GVHD. However, many patients have gotten huCART19 after have had a transplant in the past, and have not gotten GVHD, so we think the risk of this is low.

GVHD usually involves the following symptoms:

- Skin: ranges from a mild rash to severe blistering.
- Liver: ranges from mild abnormalities in liver function detected by blood testing to severe liver failure. This can lead to nausea, vomiting, loss of appetite, fluid retention, bleeding problems, and severe liver failure, and can be fatal.
- Intestine: ranges from mild diarrhea, nausea and vomiting to severe diarrhea, abdominal pain, paralysis of the bowel, bleeding from the bowel, and inability to eat.

- Bone marrow: The infused lymphocytes may attack your bone marrow cells. These cells are necessary to produce red blood cells, white blood cells, and platelets. If your red blood counts become very low, you can develop weakness, fatigue, shortness of breath and other symptoms related to anemia. This may be treated with red blood cell transfusions. If your white blood count becomes too low, you may be susceptible to serious infections. This may require hospitalization for antibiotics and other treatment. If the platelets are too low, you may be at risk for serious bleeding problems. Platelet transfusions can be given as well. It is possible that all normal bone marrow cells can be irreversibly destroyed (bone marrow aplasia). In this event, another stem cell transplant could be required. We have not seen this happen.

The severity of GVHD ranges from very mild to severe and life-threatening. If you develop GVHD you will be treated initially with steroids and possibly other medications as your condition warrants. These medications will suppress your immune system and may also make you susceptible to serious infections. The medicines could also interfere with the functioning of the huCART19 cells.

Potential for a positive HIV test and reporting of the result:

You will be tested for HIV as one of the requirements to participate in this study. Should your test be positive, the physician has an obligation to fulfill state reporting requirements for people who have tested positive for HIV. This reporting is how the Centers for Disease Control and Prevention (the CDC) is able to track the number of HIV infected individuals in the U.S. In addition, if you have a partner you will be counseled on how you, or a nurse or physician, can inform your partner of your HIV test results.

Risks associated with blood draws:

Occasionally there are risks associated with blood draws such as bruising, swelling, black and blue marks, fainting and/or infection at the site. You may also experience a decrease in hemoglobin (red blood cell number, called anemia) from having blood drawn frequently. Both the total amount of blood drawn during the study and the amount drawn at any one time will be kept to safe limits.

Risks associated with breach of confidentiality:

As with any study involving collection of data, there is the possibility of breach of confidentiality of data. Every precaution will be taken to secure participants' personal information to ensure confidentiality. At the time of participation, each participant will be assigned a study identification number. This number will be used on data collection forms, biospecimens, and in the database instead of names and other private information. A separate list will be maintained that will link each participant's name to the study identification number for future reference and communication.

Risks associated with genetic testing/analysis:

The risks related to genetic analyses can be to individuals or groups. These harms include stigmatization and insurability. To reduce this risk, only coded samples will be stored and used for future research. Information about genetic testing will not be recorded in your medical record. The Genetic Information Nondiscrimination Act is a Federal law that makes it illegal for some groups to discriminate against you based on genetic information. This law applies to all health insurance companies, group health plans, and employers with 15 or more employees.

Are there any benefits to taking part in this study?

You might benefit by having the number of cancer cells reduced. However, we cannot guarantee or promise that you will receive any direct benefit by participating in this study. The knowledge gained from this research may help doctors determine better ways to treat your type of disease.

Do you need to give your consent in order to participate?

If you decide to participate in this study, you must sign this form. A copy will be given to you to keep as a record. Please consider the study time commitments and responsibilities as a research subject when making your decision about participating in this study

What happens if you decide not to take part in this study?

Participation in this study is voluntary. You do not have to take part in order to receive care at CHOP.

If you decide not to take part or if you change your mind later there will be no penalties or loss of any benefits to which you are otherwise entitled.

Can you stop your participation in the study early?

You can stop being in the study at any time. You do not have to give a reason.

Can the study doctor take you out of the study early?

Your doctor or the study doctor may decide to take you off this study for the following reasons (this may happen before or after you have received the huCART19 cells):

- Believes that it is your best interest
- You have lab test results that have changed since screening, or your cancer or level of health have changed
- You experience side effects from the treatment that are considered too severe
- We are unable to manufacture huCART19 cells for you
- Pregnancy

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the study doctor and your regular doctor first.

What choices do you have other than this study?

There are other options for you other than this study including:

- Getting treatment or care for your leukemia without being in a study
- Some patients may be eligible to receive Kymriah™ (or CART19), which has been FDA approved for certain patients with acute lymphoblastic leukemia up to the age of 25 years old.
- Taking part in another study
- Getting no treatment

You are encouraged to discuss these options with your regular doctor as well as other trusted personal and family advisors.

What about privacy, authorization for use of Personal Health Information (PHI) and confidentiality?

We need to collect health information about you in order to conduct this study. This includes information about you from medical records and from the procedures and tests that are part of this research. Routine clinical laboratory tests performed as part of this study will appear in your medical record. We will do our best to keep your personal information private and confidential. However, we cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law.

The results of this study may be shown at meetings or published in journals to inform other doctors and health professionals. We will keep your identity private in any publication or presentation about the study.

Several people and organizations may review or receive your identifiable information. They will need this information to conduct the research, to assure the quality of the data, or to analyze the data or samples. These groups include:

- Members of the research team and other authorized staff at CHOP;
- People from agencies and organizations that perform independent accreditation and/or oversight of research; such as the Department of Health and Human Services, Office for Human Research Protections;
- The sponsor of the trial, the University of Pennsylvania, and authorized representatives;
- The Data and Safety Monitoring Board;
- Employees of the facility producing the vector or the cells for the study;
- Novartis Pharmaceuticals and its authorized agents- who are collaborating with the Sponsor (the University of Pennsylvania) on studies using CAR T-cells.
- Representatives of the National Cancer Institute (NCI), Food and Drug Administration (FDA), The Office of Biotechnology Activities, and other U.S. and international governmental regulatory agencies involved in keeping research safe for people;
- Public health authorities that are required by law to receive information for the prevention or control of disease, injury, disability or child abuse.

By law, CHOP is required to protect your health information. The research staff will only allow access to your health information to the groups listed above. By signing this document, you are authorizing CHOP to use and/or release your health information for this research. Some of the organizations listed above may not be required to protect your information under Federal privacy laws. If permitted by law, they may be allowed to share it with others without your permission.

There is no set time for destroying the information that will be collected for this study. Your permission to use and share the information and data from this study will continue until the research

study ends and will not expire. Researchers continue to analyze data for many years and it is not possible to know when they will be completely done.

While participating in this study, study staff will replace your name with a special code that identifies you. This code, along with your Study Information and biological samples, will be used by the University of Pennsylvania (Sponsor), and their representatives as described in this document and to help establish whether the study drug is safe and effective. Within the scope of this consent, the University of Pennsylvania may share your coded information, as necessary.

Can you change your mind about the use of personal information?

You may change your mind and withdraw your permission to use and disclose your health information at any time. To take back your permission, it is preferred that you tell the investigator in writing.

Dr. Shannon Maude
Children's Hospital of Philadelphia
[redacted]

In the letter, state that you changed your mind and do not want any more of your health information collected. The personal information that has been collected already will be used if necessary for the research. No new information will be collected. If you withdraw your permission to use your personal health information, you will be withdrawn from the study.

Additional Information

A Data Safety and Monitoring Board, an independent group of experts, will be reviewing the data from this research throughout the study.

You will be informed if changes to the study are needed to protect your health. You will be told about any new information that could affect your willingness to stay in the study, such as new risks, benefits or alternative treatments.

Financial Information

While you are in this study, the cost of your usual medical care – procedures, medications and doctor visits – will continue to be billed to you or your insurance.

Will there be any costs to you?

All research procedures, including the cost of making the cells and chemotherapy and its administration will be paid for by the study.

You or your insurance company will be charged for continuing medical care and/or hospitalization.

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

Will you be paid for taking part in this study?

You will receive no stipend payment or money for taking part in this study. There are no plans for you to profit from any new products developed from research done on your specimens. Some financial reimbursement is provided for the cost of travel to CHOP and lodging during your participation in this study. You will need to submit receipts for reimbursement.

Who is funding this research study?

This study is funded by CHOP internal funds.

Do any of the doctors or scientists involved with this study have a conflict of interest that may bias their decision making?

The University of Pennsylvania has a significant financial interest in technologies being evaluated in this study. Some of these technologies have been licensed to a pharmaceutical company, Novartis. As a result of the licensing relationship with Novartis, the University of Pennsylvania receives significant financial benefit. In the event that these technologies prove to be effective, the financial benefit to the University of Pennsylvania will increase.

In addition, some of the investigators involved in this study also have significant financial interests related to this research. Specifically:

1. Dr. June and Dr. Levine (scientific advisors for this study) have invented technologies that are being used and evaluated in this study. Many of these technologies have been licensed to Novartis. As a result of this licensing relationship the investigators receive significant financial benefit. In the event that these technologies prove to be effective, the financial benefit to these investigators will increase.
2. In addition, Dr. June invented the technology used to expand your cells for this study and he receives significant financial benefit related to this. This technology is licensed to a biotechnology company called Life Technologies and has been sub-licensed to Novartis.
3. One of the study investigators, Dr. Grupp, and the individuals referred to above have a patent pending on a lab test that may be used to evaluate a potential study related toxicity. This test has also been licensed to Novartis. This research study may help advance our understanding of how we can predict whether someone may experience this toxicity. If the study shows that the test may be useful for predicting adverse effects, the investigators may benefit financially. Dr. Grupp also has a consulting arrangement with the drug company Novartis.
4. Some of the investigators on this study, including the Principal Investigator, Dr. Maude, have served as consultants to Novartis. Novartis has licensed the study drug from Penn and could benefit if this study is successful. All investigators involved in this study were reviewed and approved in accordance with CHOP's Conflict of Interest policy. If you have any questions or concerns about this potential conflict of interest, you may speak to Dr. Maude, or contact CHOP's Conflict of Interest Office at [redacted].

If you would like more information, please ask the researchers or the study coordinator.

What if you have questions about the study?

If you have questions about the study, call the study doctor, Dr. Shannon Maude, at [redacted]. You may also talk to your own doctor if you have questions or concerns.

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.

The Institutional Review Board (IRB) at The Children's Hospital of Philadelphia has reviewed and approved this study. The IRB looks at research studies like these and makes sure research subjects' rights and welfare are protected. If you have questions about your rights or if you have a complaint, you can call the IRB Office at 215-590-2830.

You will get a copy of this form.

What happens if you are injured during the study?

If you are hurt or get sick from something that was done as part of this study, doctors at the clinic or hospital can arrange for emergency medical care. The Hospital does not offer financial compensation or payment for injuries due to participation in this research.

You and your insurance company will be billed for the costs of any care or injuries.

If you think you have been injured from taking part in this study, call Dr. Shannon Maude at [redacted]. She can go over things with you, let you know of resources that may be available and give you information on what you need to do. In case of injury resulting from this study, you will not lose any legal rights by signing this form.

About Using Blood and Tissue for Research

In addition to the testing outlined above, we would like to use your leftover specimens (blood, tissue, spinal fluid) for future research. This may include genetic testing and may take place while you are on study or years from now. You will not directly benefit from this additional research, but these studies may benefit patients in the future. You will not receive the results of this testing. You will not receive payment for the use of your specimens or as a result of any new products developed from research done on your specimens.

Researchers involved in this study at the Children's Hospital of Philadelphia and University of Pennsylvania, will have access to the specimens. Your specimens may be sent to other researchers, including researchers at for-profit agencies (such as Novartis Pharmaceuticals). No information directly identifying you will be included with these specimens. These specimens may be used for new research studies related to your disease or treatment with huCART19 T-cells. Your specimens will be stored at the University of Pennsylvania until all research has been completed. You have the right to withdraw any specimens from further use by contacting Dr. Shannon Maude at [redacted]. Any specimens that have already been used for research will be kept by the researchers.

Please indicate whether you will allow your data and specimens to be used for future research, including genetic testing, by putting your initials next to one of the following choices. Neither choice changes the ability to enroll in this study.

Initial	
	My data and specimens may be used for **this study only**.
	I AGREE to allow my data and specimens to be kept for use in research to learn about, prevent, treat, or cure cancer or other diseases. My data and specimens may be used for other future research studies, including genetic testing. If the data or specimens are used for future research at CHOP/Penn or are shared outside of CHOP/Penn, no information directly identifying me will be included.

Consent to Take Part in this Research Study and Authorization to Use and Disclose Health Information for the Research (English Speaking Subjects and Families)

The research study and consent form have been explained to you by:

Person Obtaining Consent	Signature of Person Obtaining Consent
	Date

By signing this form, you are indicating that you have had your questions answered, you agree to take part in this research study and if you are giving permission for a child or consent for an adult to participate in this research study, you are legally authorized to consent to the child's or adult's participation. You are also agreeing to let CHOP use and share the health information that will be collected for this study, as explained above. If you don't agree to the collection, use and sharing of health information, you cannot participate in this study.

NOTE: *A foster parent is not legally authorized to consent for a foster child's participation.*

Name of Subject	
Signature of Subject (18 years or older)	Date
Name of Authorized Representative (if different than subject)	Relation to subject: ☐ Parent ☐ Legal Guardian ☐ Legally Authorized Representative
Signature of Authorized Representative	Date

Assent to Take Part in this Research Study

For adults with diminished capacity capable of providing assent:

I have explained this study and the procedures involved to _____ in terms he/she could understand and that he/she freely assented to take part in this study.

_____
Person Conducting Assent

_____ _____
Signature of Person Conducting Assent Date

This study has been explained to me and I agree to take part.

_____ _____
Signature of Subject (optional) Date

For adults with diminished capacity unable to assent:

I certify that _____ was not capable of understanding the procedures involved in the study sufficiently to assent to study participation.

_____
Person Responsible for Conducting Assent

_____ _____
Signature of Person Responsible Date

STUDY SUMMARY SIGNATURE PAGES FOR NON-ENGLISH SPEAKING SUBJECTS

Consent to Take Part in this Research Study and Authorization to Disclose Health Information

Name of Subject

Name of Authorized Representative (if different than subject)

Relation to subject:
☐ Parent ☐ Legal Guardian
☐ Legally Authorized Representative

The research study and consent form have been explained to the subject or parent/legal guardian/legally authorized representative.

By signing this form, you are indicating that you have answered the subject's or parent's/legal guardian's/legally authorized representative's questions, they have agreed to take part in this research study and they are legally authorized to consent to their, their child's, or the adult's participation. They have also agreed to let CHOP use and share the health information as explained above. If they don't agree to the collection, use and sharing of the health information, they cannot participate in this study.

Person Obtaining Consent

Signature of Person Obtaining Consent

Date:

Witness/Interpreter

By signing this form, you are indicating that

- The information in the Summary Document as well as any additional information conveyed by the person obtaining consent was presented to the subject in a language preferred by and understandable to the subject; and
- The subject's questions were interpreted and the responses of the person obtaining consent were presented in a language preferred by and understandable to the subject.
- At the conclusion of the consent conference, the subject was asked in a language preferred by and understandable to the subject if s/he understood the information in the Summary Document as well as any additional information conveyed by the person obtaining consent (including responses to the subject's questions) and responded affirmatively.

Name of Witness/Interpreter

Signature of Witness/Interpreter

Date:

Assent to Take Part in this Research Study *(Non-English Speaking Subjects)*

For adults with diminished capacity capable of providing assent:

I have explained this study and the procedures involved to _____ in terms he/she could understand and that he/she freely assented to take part in this study.

_____
Person Obtaining Assent

_____ _____
Signature of Person Obtaining Assent Date

For adults with diminished capacity unable to assent:

I certify that _____ was not capable of understanding the procedures involved in the study sufficiently to assent to study participation.

_____
Person Responsible for Conducting Assent

_____ _____
Signature of Person Responsible Date

Witness/Interpreter

By signing this form, you are indicating that

- The information in the Summary Document as well as any additional information conveyed by the person obtaining assent was presented to the subject if they were capable of providing assent in a language preferred by and understandable to the subject; and
- The subject's questions, if they were capable of providing assent, were interpreted and the responses of the person obtaining assent were presented in a language preferred by and understandable to the subject.
- At the conclusion of the consent conference, the subject was asked in a language preferred by and understandable to the subject if s/he understood the information in the Summary Document as well as any additional information conveyed by the person obtaining assent (including responses to the subject's questions) and responded affirmatively, if they were capable of providing assent.

_____ _____
Name of Witness/Interpreter Signature of Witness/Interpreter

Date: _____