The Ohio State University Combined Consent to Participate in Research and HIPAA Research Authorization

Study Title:	**A Phase Ib Study of TGFbi NK cells and Isatuximab for myeloma relapsed/refractory to BCMA targeting therapy**
Principal Investigator:	**Elvira Umyarova, MD** 460 W. 10th Ave Columbus, OH 43210 614-293-3196 or 614-293-8000 (24 hours)
Sponsor:	**The Ohio State University**
Supplier of Isatuximab:	**Sanofi**

- **This is a consent form for research participation.** It contains important information about this study and what to expect if you decide to participate. Please consider the information carefully. Feel free to discuss the study with your friends and family and to ask questions before making your decision whether or not to participate.
- **Your participation is voluntary.** You may refuse to participate in this study. If you decide to take part in the study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your usual benefits. Your decision will not affect your future relationship with The Ohio State University. If you are a student or employee at Ohio State, your decision will not affect your grades or employment status.
- **You may or may not benefit as a result of participating in this study.** Also, as explained below, your participation may result in unintended or harmful effects for you that may be minor or may be serious depending on the nature of the research.
- **You will be provided with any new information that develops during the study that may affect your decision whether or not to continue to participate.** If you decide to participate, you will be asked to sign this form and will receive a copy of the form. You are being asked to consider participating in this study for the reasons explained below.

Key Information About This Study

The following is a short summary to help you decide whether or not to be a part of this study. More detailed information is listed later in this form.

You have been invited to take part in a clinical research study because you have multiple myeloma that has failed to respond to treatment or returned after previous treatment to BCMA-targeting therapy. This study uses a course of chemotherapy followed by infusions of natural killer (NK) cells (TiNK) in combination with the antibody Isatuximab.

NK cells are a type of white blood cell that are known to spontaneously attack cancer cells. TGFβi NK cells are NK cells made to have a higher response to tumor cells. The cells will made at the Cellular Therapy Laboratory (CTL) at the Ohio State University – James Cancer Hospital from healthy universal donor cells. The donors are recruited from the National Marrow Donor Program and undergo extensive testing to ensure that they don't have communicable diseases.

Isatuximab, also known as Sarclisa, is a monoclonal antibody medication used for the treatment of multiple myeloma. Isatuximab has been approved by the U.S. Food and Drug Administration (FDA) since 2020 for the treatment of adult patients with relapsed or refractory multiple myeloma. Isatuximab will be supplied by Sanofi.

Taking part in any clinical research study involves potential risks and benefits. You need to understand these risks and benefits to make an informed decision about whether or not to be in the study. You should ask your study doctor at any time if you have questions or concerns about this research.

Please note that participation in this trial will not impact your eligibility for a future salvage autologous stem cell transplant. The high dose chemotherapy involved in a future stem cell transplant would cause TiNK cells death and would not affect your safety. You can ask your study doctor if you have any questions.

You do not have to join this research study. You can choose to receive standard methods to treat your myeloma instead of participating on this study. If you are interested in learning more about this study, please continue to read below.

Ohio State University could benefit financially from the sale of TGFβi NK cells being tested if the product is approved by the FDA. A conflict of interest committee at Ohio State has reviewed this information and determined that the financial interest presents no additional significant risk to the study's participants. Any questions about this information can be answered by Dr. Elvira Umyarova at 614-293-3196.

Dr. Abdullah Khan, a researcher helping to perform this study, is a paid consultant for Sanofi, the manufacturer of Isatuximab, one of the study drugs being test. A conflict of interest committee at Ohio State has reviewed this information and determined that Dr. Khan's involvement presents no additional significant risk to the study's participants. Any questions about this information can be answered by Dr. Elvira Umyarova at 614-293-3196.

1. Why is this study being done?

The purpose of this study is to evaluate the response of TiNK cells in the treatment of relapsed and refractory multiple myeloma to BCMA-targeted therapy. The study will also evaluate the safety and tolerability of TiNK and isatuximab in combination.

2. How many people will take part in this study?

It is anticipated that about 27 patients may participate in this study at The Ohio State University.

3. What will happen if I take part in this study?

If you are eligible to take part in the study, agree to participate, and sign this Informed Consent Form, you will have the screening tests and procedures listed below. No study procedures will be done until after you sign this form.

Before you begin the study

Screening Assessments before treatment starts

The following routine tests and evaluations will be performed to determine if you can safely participate:

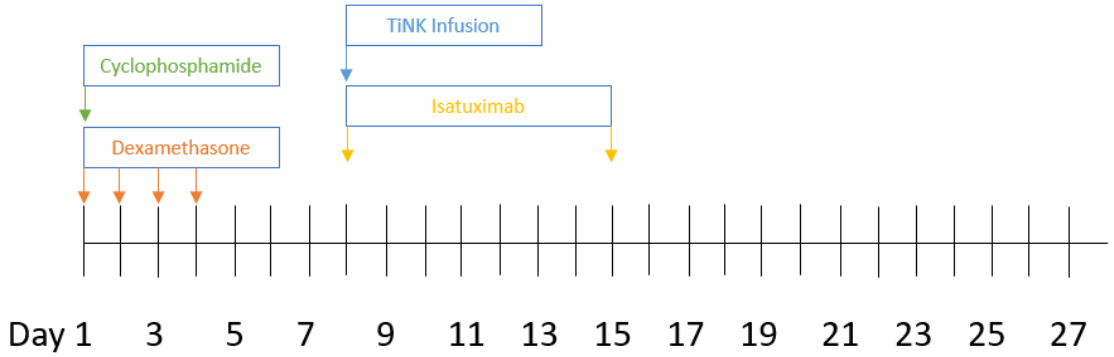
- Medical history and physical examination, including vital signs, height and weight.
- Routine blood tests to evaluate bone marrow, kidney, and liver function, as well as general health status.
- Tests to evaluate your cancer, including blood tests and imaging scans
    - Radiologic imaging will be determined by your doctor and standard of care
- Tests to evaluate heart function including an electrocardiogram (ECG) and echocardiogram (echo).
- A pregnancy test (blood) for women of childbearing potential.
- A bone marrow aspirate and biopsy

You will also be asked to complete two quality of life questionnaires about your general health, pain, fatigue, side effects of treatment, body image and future persectives. They should take approximately 10 minutes to complete.

During the study:

All treatment will be given on an outpatient basis.

Treatment will be administered in 28-day cycles. Your overall response will be assessed after every cycle. The planned course of therapy is 6 cycles. Each treatment visit to the clinic will take approximately 3-4 hours.



Cycle Days (Total of 6 planned cycles)
Day 1
You will receive the chemotherapy drug cyclophosphamide as an intravenous (IV) infusion.

You will be asked to complete two quality of life questionnaires on Day 1 of each treatment cycle. They will include questions about general health, pain, fatigue, side effects of treatment, body image and future persectives. They should take approximately 10 minutes to complete.

Days 1 – 4
You will take the steroid tablet dexamethsone orally (by mouth) once a day. It is preferred that you take this medicine in the morning with food to avoid altered sleep and an upset stomach.

Day 8
You will receive the infusion of the TiNK cells over 60 minutes. You will be monitored at the clinic for at least an hour after the completion of TiNK cell infusion. After the TiNK infusion, you will receive an infusion of isatuximab.

Day 15
You will receive a second dose of isatuximab via IV infusion.

Study Procedures:

Procedures	Screening Day -22 to -1	Start of Treatment C1D1	Study Visit 2 C1D8	Study Visit 3 C1D15	Study Visit 4 C2D1	Study Visit 5 C2D8	Study Visit 6 C2D15	Study Visit n C3-6D1	Study Visit n C3-6D8	Study Visit n C3-6D15	Off Study 30-days post C6 visit	Off study 60-days post C6 visit
Informed consent	X											

Procedures	Screening Day -22 to -1	Start of Treatment C1D1	Study Visit 2 C1D8	Study Visit 3 C1D15	Study Visit 4 C2D1	Study Visit 5 C2D8	Study Visit 6 C2D15	Study Visit n C3-6D1	Study Visit n C3-6D8	Study Visit n C3-6D15	Off Study 30-days post C6 visit	Off study 60-days post C6 visit
Demographics	X											
Medical history	X											
Medication review and physical exam	X	X			X			X			X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X
Performance status	X	X			X			X			X	X
Blood collection	X	X	X	X	X	X	X	X	X	X	X	X
Blood collection for Myeloma markers	X				X			X			X	X
Pregnancy test	X	X			X			X				
Bone marrow biopsy and aspirate research samples	X										optional	
MRD assessment*								X				
EKG and Echocardiogram	X											
Radiology/ Imaging assessment	X										X	
Cyclophosphamide infusion		X			X			X				
TiNK infusion			X			X			X			
Isatuximab infusion			X	X		X	X		X	X		
Quality of Life assessments	X	X			X			X			X	X

*MRD assessment is planned for participants suspected of attaining a complete response and is considered standard of care

Follow up
When your study treatment is over, we will follow up with you to monitor any side effects and to see how you are doing for 60 days.

4. How long will I be in the study?

Each treatment "cycle" will last 28 days and there are 6 planned treatment cycles. There are follow-up visits at 30 days and 60 days after the last dose After you complete the therapy, you may be treated by your cancer doctor.

You will be monitored through medical records and other sources for overall survival for up to two years following your last visit on the study.

5. Can I stop being in the study?

You may leave the study at any time. If you decide to stop participating in the study, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled. Your decision will not affect your future relationship with The Ohio State University.

6. What risks, side effects or discomforts can I expect from being in the study?

As with all research studies, the study treatment and study procedures may involve unknown risks. Any drug can have temporary and/or permanent side effects and can cause unforeseen side effects. One risk is that you may get a study drug that does not help treat your disease or that makes your condition or disease worse.

You may or may not have side effects from the study treatment or procedures used in this study. Side effects can vary from mild to very severe and may vary from person to person. All patients taking part in the study will be watched carefully for any side effects.

Here are important points about side effects:

- Some side effects may go away soon, some may last a long time, and some may never go away.
- Some side effects may interfere with your ability to have children and may cause fetal harm if you become pregnant.
- Some side effects may be serious and may even result in death.

You need to tell your doctor or a member of the study team immediately if you experience any side effects. The study doctor may be able to treat some side effects and possibly adjust the study treatment to try to reduce side effects.

If you live far away from the study site or for other reasons cannot travel to the study site, you need to go to your local healthcare providers or local emergency service.

The study treatment may affect how different parts of your body work, such as your liver, kidneys, heart, and/or blood. The study doctor will be testing your blood and will let you know if changes occurred that may affect your health.

There have been research studies with TiNK cells similar to this study; however this is an early study of TiNK cells in humans, so its side effects are not well documented.

Risks of Cyclophosphamide

Cyclophosphamide is a commonly used chemotherapy drug and is available without being on a research study. Risks associated with cyclophosphamide may include:

Common

- Absence of menstrual cycles which may decrease the ability to have children
- Blood in urine
- Feeling tired
- Hair loss, skin changes, rash, change in nails
- Infection, especially when white blood cell count is low
- Nausea, vomiting, diarrhea, loss of appetite, pain in belly
- Sores in mouth

Less Common

- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Decrease in platelets which may cause bleeding
- Decrease in red blood cells, which may require blood transfusions
- Loss or absence of sperm which may lead to an inability to father children

Rare, but may be serious

- A new cancer
- Damage to the heart or heart failure which may cause shortness of breath, swelling, cough, or tiredness
- Scarring of the lungs which may cause shortness of breath, fluid around the lungs
- Swelling of the brain which may cause dizziness, confusion

Risks of Dexamethasone

Dexamethsone is a commonly used steroid and is available without being on a research study. Serious risks associated with dexamethasone may include confusion or mood changes, stomach ulcers, high blood sugar or worsening diabetes, infection, formation of cataracts, and muscle weakness.

Other risks associated with dexamethasone may include feeling uncomfortable or burning around your stomach, irritation of your stomach, swelling, new or worsening high blood pressure, and having trouble falling asleep or staying asleep.

Risks of Isatuximab

Isatuximab is FDA approved for the treatment of relapsed/refractory multiple myeloma. Possible risks associated with Isatuximab may include:

Common (≥20% occurrence):

- Infusion-related reactions such as shortness of breath, cough, chills, and nausea
- Pneumonia
- Upper respiratory tract infection
- Diarrhea
- Blood abnormalities (low white blood cell count, low red blood cell count, low blood platelets, liver enzyme increase, and creatinine increase) (very common, can be serious)
- Fatigue (25%)

- Cough (25%)

Less common

- Nausea
- Vomiting
- Back pain
- Headache
- Bone pain
- Decreased appetite
- Chills

Before the infusion, medications are given to lessen the risk of an infusion reaction.

Risks Associated with TGFβi NK Cells

There have been research studies with TiNK cells similar to this study; however this is an early study of TiNK cells in humans, so its side effects are not well documented. The common and less common side effects are expected to occur in the first 24 hours after NK cell infusion; side effects can be treated with supportive care and are expected to resolve in 72 hours.

Common (>20% occurrence):

- Flu like symptoms, including fever, chills, cough, trouble breathing, muscle pain, fatigue, headache.
- Unusual taste or odor, increased or decreased blood pressure, fast heart rate and headache.

Less Common (≤20% occurrence):

- Infusion reactions including fever, chills, cough, trouble breathing, low oxygen levels, fluid in lungs, low blood pressure, fast heart rate, bronchospasm (tightening of the muscles that line the airways (bronchi) in your lungs), rash, severe itching, muscle pain, headache, blood in urine, poor kidney function.

Rare (≤3% occurrence):

- Infection from contamination of NK cells with bacteria is not expected. Manufacturing processes and release testing are designed to prevent this occurrence but is still possible. Infection in immunocompromised patients may be life-threatening.
- NK cells could attack your normal cells and cause damage to your body, like skin rash, liver damage, and/or damage to your stomach and intestines. Trials with similar NK cell products have not commonly reported this type of reaction.
- Cytokine release syndrome (CRS)- occurs very rarely. Symptoms of CRS may include fever, low blood pressure, and low blood oxygen level.
- Cytomegalovirus (CMV) positive donors are selected for the manufacturing of TiNK cells. The risk of the CMV virus passing from the donor to the recipient via the NK cell product, although very small, cannot be excluded.
- Tumor lysis syndrome can cause blood abnormalities (for example, high levels of potassium, calcium, uric acid, and phosphate) which may damage organs, such as the heart, kidneys, and liver.

- Risk of tumor inflammation- swelling and inflammation of tumors may cause headache, confusion, impaired coordination, seizures, or altered mental status

These rare adverse events are possible but not expected, however, may be severe and may occur with delayed onset.

Risks due to procedures

Risks Associated with Blood Draw
Risks of blood draws include mild pain or discomfort, bruising and swelling around the puncture site, dizziness or fainting, or infection (rare).

Risks Associated with Echocardiogram
There is no pain or discomfort during the test; however, the gel may cause minor skin reactions, such as redness or itching.

Risks Associated with Bone Marrow Biopsy
For this procedure, a numbing drug is injected into the skin over one of your hipbones. A needle is then inserted into the hipbones and a small piece of bone is removed. The risks may include:

- Moderate pain and discomfort
- Bleeding at the biopsy site
- Scarring at the biopsy site
- Rarely, an infection at the biopsy site
- Rarely, nerve injury at the biopsy site

Reproductive risks
The treatments (Cyclophosphamide and Isatuximab) used in this trial have clear evidence of harm to an unborn baby. We do not know whether the study drug, TiNK cells, might hurt an unborn child. For this reason, woman who can get pregnant and men with partners who can become pregnant will be asked to practice a highly effective method of birth control while participating in this study and considered medically acceptable by the study doctor for up to 6 months after study treatment ending. The research staff will give recommendations for highly effective contraception methods. **Notify your study doctor immediately if you become pregnant or father a child during the study.**

If your partner becomes pregnant, it may be critical to share information regarding your participation in this research study with that person. Your study doctor should also be told if this happens. The study drug sponsor may want to collect data on your partner's pregnancy.

If you become pregnant during the study, your study doctor may ask to collect information on:

- the outcome of your pregnancy including spontaneous or voluntary termination,
- details of the birth (full-term, premature, or involves complications),

- the presence or absence of any birth defects, abnormalities, or complications, and
- the health status of your child.

Certain drugs may reduce the effectiveness of hormonal birth control treatments during and up to 30 days after discontinuation of these concurrent therapies. Please talk to your doctor for further information about birth control treatments.

You must inform the study doctor, if at any time during the study when

- your birth control method changes, or
- you experience a problem with your current birth control method

If your ability to become pregnant changes (for example, you have an IUD removed, accidentally miss taking any of your birth control pills, or enter menopause), you must inform and discuss with the study doctor or nurse about other birth control methods.

7. What benefits can I expect from being in the study?

There is no guarantee that this treatment will benefit you. This treatment regimen may also be harmful to you. However, the benefits could be an easing of symptoms, decrease in the amount of cancer suggestive of improvement in your cancer, prolonged disease-free remission and/or survival or increased knowledge about this cancer treatment in patients with myeloma. This information could benefit patients in the future.

8. What other choices do I have if I do not take part in the study?

You may choose not to participate without penalty or loss of benefits to which you are otherwise entitled. If you choose not to participate in this study, other treatments you qualify for will be discussed with you.

Other treatment options may include:

- Getting treatment or care for your cancer without being in a study. This may include FDA approved standard of care treatment according to National Comprehensive Cancer Network (NCCN) guidelines.
- Taking part in another study
- Getting no treatment
- Getting comfort care, also called palliative care

9. What are the costs of taking part in this study?

The study drugs TiNK cells and isatuximab will be supplied by the sponsor and will not be billed to you or your insurance company. You and/or your insurance company will not be billed for the cost of any tests or procedures that are required as part of this research study *and* are outside the standard of care for your condition.

You and/or your insurance company *will* need to pay for the costs of your regular medical care you get as part of the study, just as you would if you were getting the usual care for your condition. This includes:

- The drugs cyclophosphamide, dexamethasone, and pre-medications
- The clinic visits with your doctor, the echocardiograph and radiologic imaging.
- The costs of administering the study drugs, tests, exams, procedures, and drugs that you get during the study to monitor your safety and prevent and treat side effects.
- Your insurance co-payments, coinsurance, and/or deductibles.

Participating in this research study may lead to additional costs to you. In some cases, it is possible that your insurance company will not pay for these costs because you are taking part in a research study.

Talk to your insurance company and make sure that you understand what your insurance pays for and what it doesn't pay for if you take part in this study. Also, find out if you need approval from your insurance company before you can take part in a research study.

Ask your doctor, nurse, or study coordinator for help finding the right person to talk to if you are unsure which costs will be billed to you or your insurance company.

10. Will I be paid for taking part in this study?

You will not receive payment for taking part in this study.

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

If you suffer an injury from participating in this study, you should notify the researcher or study doctor immediately, who will determine if you should obtain medical treatment at The Ohio State University Wexner Medical Center.

The cost for this treatment will be billed to you or your medical or hospital insurance. The Ohio State University has no funds set aside for the payment of health care expenses for this study.

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

If you choose to participate in the study, you may discontinue participation at any time without penalty or loss of benefits. By signing this form, you do not give up any personal legal rights you may have as a participant in this study.

You will be provided with any new information that develops during the research that may affect your decision whether or not to continue participation in the study.

You may refuse to participate in this study without penalty or loss of benefits to which you are otherwise entitled.

An Institutional Review Board responsible for human subjects research at The Ohio State University reviewed this research project and found it to be acceptable, according to applicable state and federal regulations and University policies designed to protect the rights and welfare of research participants.

13. Will my de-identified information (and bio-specimens) be used or shared for future research?

No.

14. Will my study-related information be kept confidential?

Efforts will be made to keep your study-related information confidential. However, there may be circumstances where this information must be released. For example, personal information regarding your participation in this study may be disclosed if required by state law.

Also, your records may be reviewed by the following groups (as applicable to the research):

- Office for Human Research Protections or other federal, state, or international regulatory agencies;
- U.S. Food and Drug Administration;
- The Ohio State University Institutional Review Board or Office of Responsible Research Practices;
- The sponsor supporting the study, their agents or study monitors; and
- Your insurance company (if charges are billed to insurance).
- Nationwide Children's Hospital

If we find information that significantly impacts your health, we **will** share it with you. This information may be relayed to you by phone, email, mail, or routine clinic visit. You may be asked to sign a new consent form that includes the new information.

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

15. HIPAA AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES

I. What information may be used and given to others?

- Past and present medical records;
- Research records;
- Records about phone calls made as part of this research;
- Records about your study visits;
- Information that includes personal identifiers, such as your name, or a number
- Information gathered for this research about:

HIV / AIDS
Hepatitis infection
Sexually transmitted diseases
Other reportable infectious diseases
Physical exams
Laboratory, x-ray, and other test results
Diaries and questionnaires
The diagnosis and treatment of a mental health condition

- Records about any study drug you received

II. Who may use and give out information about you?

Researchers and study staff.

III. Who might get this information?

- The sponsor of this research. "Sponsor" means any persons or companies that are:
  - working for or with the sponsor; or
  - owned by the sponsor.
- Authorized Ohio State University staff not involved in the study may be aware that you are participating in a research study and have access to your information;
- If this study is related to your medical care, your study-related information may be placed in your permanent hospital, clinic, or physician's office record;
- Others: Sanofi, the pharmaceutical supplier of Isatuximab, and Nationwide Children's Hospital

IV. Your information <u>may</u> be given to:

- The U.S. Food and Drug Administration (FDA), Department of Health and Human Services (DHHS) agencies, and other federal and state entities;
- Governmental agencies in other countries;
- Governmental agencies to whom certain diseases (reportable diseases) must be reported; and
- The Ohio State University units involved in managing and approving the research study including the Office of Research and the Office of Responsible Research Practices.

V. Why will this information be used and/or given to others?

- To do the research;
- To study the results; and
- To make sure that the research was done right.

VI. When will my permission end?

There is no date at which your permission ends. Your information will be used indefinitely. This is because the information used and created during the study may be analyzed for many years, and it is not possible to know when this will be complete.

VII. May I withdraw or revoke (cancel) my permission?

Yes. Your authorization will be good for the time period indicated above unless you change your mind and revoke it in writing. You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the researchers. If you withdraw your permission, you will not be able to stay in this study. When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others.

VIII. What if I decide not to give permission to use and give out my health information?

Then you will not be able to be in this research study and receive research-related treatment. However, if you are being treated as a patient here, you will still be able to receive care.

IX. Is my health information protected after it has been given to others?

There is a risk that your information will be given to others without your permission. Any information that is shared may no longer be protected by federal privacy rules.

X. May I review or copy my information?

Signing this authorization also means that you may not be able to see or copy your study-related information until the study is completed.

16. Who can answer my questions about the study?

For study questions, concerns, or complaints, to withdraw consent and HIPAA authorization, or if you feel you have been harmed as a result of study participation, you may contact

Dr. Elvira Umyarova, MD
460 W. 10th Ave
Columbus, OH 43210

For questions related to your privacy rights under HIPAA or related to this research authorization, please contact

HIPAA Privacy Manager
The Ohio State University
Medical Center
Suite E2140
600 Ackerman Road
Columbus, OH 43202
614-293-4477

For questions about your rights as a participant in this study or to discuss other study-related concerns or complaints with someone who is not part of the research team, you may contact the **Office of Responsible Research Practices at 1-800-678-6251.**

If you are injured as a result of participating in this study or for questions about a study-related injury, you may contact **Dr. Elvira Umyarova at 614-293-3196 or 614-293-8000 (24 hours).**

Signing the consent form

I have read (or someone has read to me) this form and I am aware that I am being asked to participate in a research study. I have had the opportunity to ask questions and have had them answered to my satisfaction. I voluntarily agree to participate in this study.

I am not giving up any legal rights by signing this form. I will be given a copy of this combined consent and HIPAA research authorization form**.**

Printed name of participant	**Signature of participant**
	AM/PM
	Date and time
Printed name of person authorized to consent for participant (when applicable)	**Signature of person authorized to consent for participant (when applicable)**
Relationship to the participant	**AM/PM**
	Date and time

Investigator/Research Staff

I have explained the research to the participant or his/her representative before requesting the signature(s) above. There are no blanks in this document. A copy of this form has been given to the participant or his/her representative.

Printed name of person obtaining consent	**Signature of person obtaining consent**
	AM/PM
	Date and time

Witness(es) - *May be left blank if not required by the IRB*

Printed name of witness	**Signature of witness**
	AM/PM
	Date and time
Printed name of witness	**Signature of witness**
	AM/PM
	Date and time