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Approved by the Beth Israel Deaconess Medical Center Committee on Clinical Investigations:

Consent Approval Date: 08/08/022

Protocol Number: 2021P000715

BETH ISRAEL DEACONESS MEDICAL CENTER
APPROVED BY THE COMMITTEE ON CLINICAL INVESTIGATIONS
08/07/2023
APPROVAL EXPIRATION DATE

INFORMED CONSENT FORM TO TAKE PART IN A RESEARCH STUDY

SUBJECT'S NAME:
TITLE OF RESEARCH PROTOCOL: Self-Administered Nitrous Oxide (SANO) During Transrectal Prostate Biopsy to Reduce Patient Anxiety and Pain
PRINCIPAL INVESTIGATOR: Heidi Rayala, MD PhD
PROTOCOL NUMBER: 2021P-000715

KEY INFORMATION

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

Why am I being invited to take part in a research study?
We invite you to take part in a research study because you are scheduled to have a prostate biopsy soon.

What should I know about a research study?
- Someone will explain this research study to you.
- Whether or not you take part is up to you.
- Your participation is completely voluntary.
- You can choose not to take part.
- You can agree to take part and later change your mind.
- Your decision will not be held against you.
- Your refusal to participate will not result in any consequences or any loss of benefits that you are otherwise entitled to receive.
- You can ask all the questions you want before you decide.
- If you choose not to take part, or if you leave the study, your decision will in no way harm your relationship with any member of the research team or any other individuals at Beth Israel Deaconess Medical Center.

Why is this research being done?
The transrectal prostate needle biopsy is a very common procedure in the US. For some patients, a prostate biopsy can be associated with anxiety or discomfort. Nitrous oxide (or laughing gas) is a well-known sedative which is frequently used in dental offices and for pediatric procedures to alleviate a patient's anxiety and pain. We would like to determine whether administration of nitrous oxide at the time of prostate biopsy will improve a patient's experience of care.

How long will the research last and what will I need to do?
We expect that you will be in this research study for up to seven days after your prostate biopsy.

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You will either receive self-administered nitrous oxide or oxygen during your prostate biopsy. This administration of the gas will be done by our staff and you won't be responsible for administering the nitrous oxide. We will adjust the dose based on your comfort level but you won't be allowed to request more gas. To check on the effectiveness of the treatment, we will ask you to answer questions regarding your demographics, medical history, current health condition, anxiety and pain.

More detailed information about the study procedures can be found under ***"DESCRIPTION OF STUDY DETAILS".***

Is there any way being in this study could be harmful to me?
There are some potential side effects when using nitrous oxide. About 1 in 200 patients who are given nitrous oxide can experience mild nausea and vomiting from the nitrous oxide gas. Other people have reported sweating, drowsiness, or lightheadedness when using nitrous oxide.

More detailed information about the risks can be found under ***"RISKS AND DISCOMFORTS".***

Will being in this study help me in any way?
We cannot promise any benefits to you or others from your taking part in this research. However, possible benefits include decreased anxiety and pain during your prostate biopsy. The results of the research will improve scientific understanding of the impact of self-administered nitrous oxide on anxiety and pain for prostate biopsy and other medical procedures.

What happens if I do not want to be in this research?

Participation in research is completely voluntary. You can decide to participate or not to participate. Your alternative to participating in this research is not to participate and you will receive the standard pain control measures done for prostate biopsies at BIDMC.

Currently we do not offer Nitrous Oxide to patients outside of this research study. However, one option for men who are concerned about the biopsy is to receive a prescription for an anti-anxiety pill (a benzodiazepine) that they can take before the procedure. However, if you decide to take the anti-anxiety pill, you will not be eligible to be part of this research study.

DETAILED INFORMATION SECTION

Please read this consent form carefully and ask the investigators or study staff to explain any words or information that you do not clearly understand. Once you read this consent form and understand what your participation in this study will involve, you will be asked to sign this form if you wish to take part. You will be given a signed copy of the form to keep for your records.

DISCLOSURE OF SPECIAL INTERESTS OF BIDMC AND INVESTIGATORS

This study is being conducted by Dr. Heidi Rayala and is funded by Sedation Systems LLC. The funding agency in this study, Sedation Systems LLC, is paying Beth Israel Deaconess Medical Center to perform this research. BIDMC and Dr. Rayala have no additional interests in this research project.

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WHOM TO CONTACT IF YOU HAVE QUESTIONS OR PROBLEMS

If you have any questions, concerns or complaints about this research or experience any problems, you should contact Dr. Heidi Rayala at [617] 667-3739.

PURPOSE

Over one million patients have transrectal prostate biopsies in the US every year. Although generally well tolerated, some men experience some anxiety and pain while having a biopsy. Nitrous oxide, also known as laughing gas, is a safe drug commonly used by dental and pediatric offices to reduce anxiety and pain. It is also being adopted in many Urology clinics across the country for office based procedures.
We are doing this study to understand whether using nitrous oxide reduces anxiety and pain and improves the patient experience during prostate biopsy. In addition, we want to see whether it is practical for urologists to use nitrous oxide for their procedures. If we find that nitrous oxide reduces anxiety and pain for prostate biopsy, it might lead to improvements to anxiety and pain for future patients.

As part of the study, we are using the The Nitrouseal® system. Nitrouseal® is a gas mask that releases nitrous oxide in a safe manner similar to other gas masks for medical gases, while preventing the gas from leaking into the air. It is different from other similar devices as it can be connected to an FDA-cleared exhaled waste gas scavenger, the Miniscav®. Together, they prevent nitrous oxide from leaking out and affecting clinical staff. This is important because long-term exposure to nitrous oxide may have negative effects on health. Nitrouseal® will be used to deliver the gas you receive during your biopsy.

STUDY PARTICIPANTS

You have been asked to be in the study because you are scheduled to have a prostate biopsy.

Approximately 130 people will take part in this study at Beth Israel Deaconess Medical Center.

DESCRIPTION OF STUDY DETAILS

If you agree to be in this study, you will be in this research study for about one week.

After you sign the consent form, the following things will happen:

1. Screening Procedures: Screening procedures are tests and procedures that will be done to

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determine if you are eligible to take part in the research study. For this research study, the screening procedures include: the completion of a baseline questionnaire. This questionnaire will ask you information about your demographics, medical history, and other relevant study information. Based on your answers, you may not be found to qualify for the study. In that scenario, your participation in the study will end and you will not need to do any other procedures as part of the study.

2. Randomization Procedures: It is not clear at this time which of the treatments in this study would be better for you. For this reason, the treatment plan offered to you will be picked by chance [like the flip of a coin]. You will not be able to choose which treatment you receive. The chances of receiving either of the treatments are approximately equal. After the randomization, you will be assigned to one of the following groups:

   A) Self-Administered Nitrous Oxide (SANO)

   B) Oxygen (Placebo)

   If one treatment arm is found to be less effective than the other while you are taking part in the study, you will be informed and further treatment will be discussed.

   Depending upon the group to which you are assigned, you may receive a placebo (i.e. oxygen) instead of the study drug. A placebo is an inactive treatment that looks like the study drug, but a placebo contains no active medication. Placebos are used to help determine if the results of the study are truly from the study drug. You will not know whether you will be receiving the study drug or the placebo. However, this information can be learned in case of an emergency.

3. Research Procedures: If you qualify to take part in this research study and agree to participate, you are required to have someone to drive you home after the procedure. On the day of the biopsy, you will undergo these research procedures:

   - On the day of your biopsy, a member of the research team will ask you some questions about your anxiety and pain before your procedure. We expect the questionnaires to take 30 minutes of your time.
   - The length of the procedure is not expected to take longer, but there will be an additional 5 minutes to set up the nitrous oxide or oxygen before the biopsy begins.
   - During your biopsy, you will wear the Nitrouseal® mask. Please note you will be able to place and remove the mask as needed. You will be able to converse during the procedure and this will help the research team adjust amount of gas you receive.
   - Oxygen will be released through the mask until the Urologist is ready to insert the rectal probe. You will be asked to take several deep breathes at this time. If you were assigned to the SANO group, nitrous oxide will be released instead of oxygen. As

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mentioned before, you will not be told whether or not you will receive nitrous oxide unless there is an emergency. At the end of the procedure, nitrous oxide (if used) will be stopped and only oxygen will continue to flow through the mask. You will continue to wear the mask for a few minutes while you breathe normal oxygen. A trained and qualified staff member will monitor your condition and oxygen levels throughout the biopsy to ensure your safety and well-being.
    - You may choose to remove the mask and stop your treatment with the gas for any reason at any time. Please inform the monitor in that situation and they will assist you.
- After you are moved to the recovery room following your biopsy, we will ask you some questions on your anxiety and pain. We will also check with you about any potential side-effects at this time.
- We will ask your Urologist how easy or difficult it was to perform the biopsy.
- We expect you to be fully recovered from the effects of SANO within five minutes of stopping the gas. While in the recovery room, the study team will administer two brief cognitive tests to assess your ability to safely drive home. These tests will primarily evaluate your hand-eye coordination.
- If you feel you do not feel comfortable driving after your biopsy, and you do not already have an escort planned, we will coordinate with you and your emergency contact to arrange a ride home.

4. Monitoring/Follow-Up Procedures. Procedures performed to evaluate the effectiveness and safety of the research procedures are called "monitoring" or "follow-up" procedures. For this research study, the monitoring/follow-up procedures include:

    - Members of the research team will review your medical record to track your health status and any potential side effects.

Study Visit Timeline	Prior to Day of Biopsy	Before Biopsy	During Biopsy	After Biopsy	7 Days After Biopsy
Consent /Assent	X				
Online Questionnaire	X				
Pain and Anxiety Measurements		X		X	
Study Treatment			X		
Safety Follow-Up					X

Individual Research Results

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Your study doctor will disclose any clinically relevant research results to you, including if we find any unexpected side effects of the nitrous oxide.

Most tests done on samples in research studies are only for research and have no clear meaning for health care. The research testing done in this study is just a stepping stone to learning more about the use of nitrous oxide during prostate biopsy.

While you should not expect to receive any results from the research testing, if we find that research results from your sample are of high medical importance, we may attempt to contact your medical provider to discuss the results. In some situations, follow up testing might be needed in a Clinical Laboratory Improvement Amendments (CLIA) certified clinical lab. You and your medical insurer may be responsible for the costs of these tests and any follow up care, including deductibles and co-payments. It is possible that you will never be contacted with individual research findings. This does not mean that you don't have or won't develop an important health problem.

Information and Biological Samples
Your information and biological samples will be used and shared with the sponsor and the researchers involved in this study to conduct the research. The consent form provides information on who will have access to identifiable information and identifiable biological samples during the study. We also want you to know that your information or biological samples may be stripped of any identifiers (for example your name, medical record number or date of birth) and used for future research studies or distributed to another researcher for future research studies without additional informed consent. BIDMC researchers or other third party researchers may use your information and samples in other scientific research, product testing or commercial development. It is unknown whether a product will ultimately be developed from the research described in this consent form or from any such work that may be performed by BIDMC or other third parties receiving your information or biological samples. In signing this consent form, you are acknowledging and voluntarily consenting to the possibility that your information and biological samples may be used for commercial purposes. For example, your samples and information may be used to develop a new product or medical test to be sold. BIDMC and other researchers may benefit if this happens. There are no plans to pay you if your samples and information are used for this purpose.

If your identifiers are removed, we will not be able to destroy or remove your information or biological samples from distributed information or samples. As part of this research program and as further explained in this form, samples of your tissue and/or information about your medical history may be provided to other researchers and/or outside collaborators.

RISKS AND DISCOMFORTS
As a result of your participation in this study, you are at risk for side effects listed in this section. You should discuss these with the investigator and with your regular doctor if you choose.

<u>More Common</u>

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There are no common risks associated with the study.

Less Common
There are no less common risks associated with the study.

Rare
The following rare risks are associated with the use of nitrous oxide:

- About 1 in 200 patients experience mild nausea and vomiting.
- Other people have reported tachycardia, facial flushing, sweating, drowsiness, or lightheadedness when using nitrous oxide.

The following rare risks are associated with the use of oxygen:

- Pure oxygen at high pressures can cause nausea, dizziness, muscle twitching. These side effects are not expected at the concentration we will be administering.

With any inhaled gas, there can be a concern of hypoxia or apnea with administration of nitrous oxide. This event has not been routinely reported in the literature as a risk or side effect of nitrous oxide. However, this will be one of the side effects that we will be most interested in following. Therefore, continuous oxygen saturation and heart rate monitoring will be done by the member of the study team assisting with nitrous oxide administration.

Loss of confidentiality

There is the potential for loss of confidentiality by participating in this study. Every effort will be made to protect the confidentiality of your identifiable information.

CONFIDENTIALITY

Information learned about you during this research program will be maintained confidentially by the research staff as described in this form.

Information learned from your participation in this study and from your medical record may be reviewed and photocopied by the Food and Drug Administration (FDA) and/or other federal and state regulatory agencies, and by the device manufacturer, Sedation Systems, LLC., accreditation agencies, the Committee on Clinical Investigations, the Human Subjects Protection Office and others involved in research administration of the Beth Israel Deaconess Medical Center. Information resulting from this study and from your medical record may be used for research purposes and may be published; however, you will not be identified by name in such publications.

MEDICAL RECORD

A copy of this consent form and information collected during this research may become part of your

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medical record, if the information is relevant to the care you receive at Beth Israel Deaconess Medical Center. Medical records are considered permanent records; therefore, information cannot be deleted from the record. Medical records are available to health care professionals at Beth Israel Deaconess Medical Center and may be reviewed by staff when carrying out their responsibilities, as well as by external parties such as health care insurers and others in certain circumstances. If you are not currently a patient at Beth Israel Deaconess Medical Center and do not have a medical record at Beth Israel Deaconess Medical Center, one may be created for you for your participation in this research. You may also be required to register as a patient of Beth Israel Deaconess Medical Center in order to participate in this research.

POSSIBLE BENEFITS

It is not possible to predict whether you will benefit directly from participation in this study. However, your participation may help others in the future as a result of knowledge gained from the research. Use of Nitrous Oxide may possibly decrease anxiety and pain during your prostate biopsy. The results of the research may improve scientific understanding of the impact of self-administered nitrous oxide on anxiety and pain for prostate biopsy and other medical procedures.

OTHER AVAILABLE OPTIONS

Taking part in this study is voluntary. Instead of being in this study, you have the following options: Your alternative to participating in this research is not to participate and undergo your prostate biopsy per your urologist's standard of care. This includes the use of pain control measures that they normally use.

If you are concerned about the biopsy you may receive a prescription for an anti-anxiety pill (a benzodiazepine) that can be taken before the procedure. However, if you decide to take the anti-anxiety pill, you will not be eligible to be part of this research study.

It is important to note that it is possible to get nitrous oxide at other institutions even if you do not take part in the study. Please be aware that not all doctors may agree to prescribe this drug for you, and health insurance companies may not pay for the drug when it is prescribed for prostate biopsies.

This research study is not meant to diagnose or treat medical problems not specifically stated in this informed consent document. Participation in this research study does not take the place of routine physical examinations or visits to your regular doctor.

We recommend that you discuss these and other options with the investigator and your regular doctor so that you can make a well-informed decision about participating in this study.

IF YOU DECIDE NOT TO TAKE PART IN THE STUDY

Participation in this study is voluntary. You have the right to decide not to take part in this study. If you choose to participate, you have the right to leave the study at any time. Your decision to not

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participate will not result in any penalties or loss of benefits to you. The investigators will tell you about new information that may affect your willingness to stay in this study.

If you decide not to participate in the study or decide to leave the study early, your decision will not affect your relationship with the research team or any other individual at Beth Israel Deaconess Medical Center.

INVESTIGATORS RIGHT TO STOP THE STUDY

The investigators have the right to end your participation in this study if they determine that you no longer qualify to take part, or if it would be dangerous for you to continue, or if you do not follow study procedures as directed by the investigators. Beth Israel Deaconess Medical Center or the funding source may stop the study at any time.

COSTS AND/OR PAYMENTS TO YOU

COSTS COVERED BY STUDY

You will not be charged for the medical gases, study device and treatment that are part of this research study. However, you and your insurance company will be charged for other tests, procedures or medications that are considered standard for a prostate needle biopsy.

CO-PAYMENT/DEDUCTIBLE STATEMENT

You will be responsible for any co-payments or deductibles that are standard for your insurance coverage.

PAYMENTS TO YOU:

You will not be paid for participating in this study.

COST OF RESEARCH RELATED INJURY:

If you are injured as a direct result of your participation in this study, you should contact the Investigator at the number provided under the section "Who to Call if You Have Questions" in this form. You will be offered the necessary care to treat your injury. We reserve the right to bill your insurance company or the sponsor, if appropriate, for the care you get for the injury. We will try to get these costs paid for, but you may be responsible for some of them. You may be responsible for all co-payments and deductibles required under your insurance. At this time there is no plan to reimburse you for items such as lost wages or lost time from work. By signing this consent form you have not given up any legal rights.

AUTHORIZATION FOR USE AND DISCLOSURE OF YOUR PROTECTED HEALTH INFORMATION

As part of this study, we will be collecting, using and sharing with others information about you.

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Please review this section carefully as it contains information about the federal privacy rules and the use and disclosure of your information.

DESCRIPTION OF PROTECTED HEALTH INFORMATION [PHI]

By signing this informed consent document, you are allowing the investigators and other authorized personnel to use and disclose health information about you. This may include information about you that already exists (for example: your medical records and other sources of health information, demographic information, and the results of any laboratory tests as well as any new information generated as part of this study. This is your Protected Health Information.

PEOPLE/GROUPS AT BIDMC WHO WILL SHARE AND USE YOUR PROTECTED HEALTH INFORMATION

Your Protected Health Information may be shared with and used by investigators working on this study, including the supporting research team (such as research assistants and coordinators, statisticians, data managers, laboratory personnel, pharmacy personnel, and administrative assistants), and may also be shared with and used by other health care providers at BIDMC who have treated you in the past and have information relevant to the research, or who provide services to you in connection with the research. Your Protected Health Information may also be shared with the members and staff of the Committee on Clinical Investigations of Beth Israel Deaconess Medical Center, which is responsible for reviewing studies for the protection of the research subjects, so that it can carry out its oversight responsibilities with respect to the study.

PEOPLE/GROUPS OUTSIDE OF BIDMC TO WHOM YOUR PROTECTED HEALTH INFORMATION WILL BE DISCLOSED (SHARED) AND WHO MAY USE YOUR PROTECTED HEALTH INFORMATION

We will take care to maintain confidentiality and privacy about you and your Protected Health Information. We may share your Protected Health Information with the following groups so that they may carry out their duties related to this research study:

- The funding source and/or sponsor of this study, Sedation Systems, LLC., and, where applicable, the people and companies that the funding source and/or sponsor use to oversee, administer, or conduct the research (for example, clinical research organizations are companies that are sometimes hired by research sponsors to help manage and run a clinical research study)
- The other hospitals and medical centers taking part in this study and research collaborators at those institutions.
- Other research collaborators and supporting research team members taking part in this study
- Any external health care providers who provide services to you in connection with this research
- Laboratories not affiliated with BIDMC that are involved in conducting tests related to the research
- Statisticians and other data monitors not affiliated with BIDMC
- The members and staff of any other IRBs (beyond the BIDMC Committee on Clinical Investigations) that oversee the research

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- Centralized data collectors
- Your health insurance company
- The Food and Drug Administration [FDA], the Department of Health and Human Services [DHHS], the National Institute of Health [NIH], the Office for Human Research Protections [OHRP], and other federal and state agencies that may have jurisdiction over the research
- Hospital and Clinical Research Accrediting Agencies
- Data and Safety Monitoring boards that oversee this study (if applicable)

Those who receive your Protected Health Information during the course of the research may not be required by the federal privacy regulations to protect it, and they may make further disclosures to others and use your information without being subject to penalties under those laws.

PURPOSE: WHY WE ARE USING AND SHARING YOUR PROTECTED HEALTH INFORMATION

The reason for using and sharing your Protected Health Information is to conduct and oversee the current, secondary, and future research described in this Informed Consent Document. There are many other reasons beyond the research for which BIDMC may use or disclose your Protected Health Information. Not all of these reasons require your express written authorization. For example, we will use and share your Protected Health Information to ensure that the research meets legal, institutional and accreditation requirements and to conduct public health activities. The various ways in which BIDMC may use and disclose your protected health information without your authorization are explained in a document called the Notice of Privacy Practices. If you have not received a copy of BIDMC's Notice of Privacy Practices, please ask us for one and review it before signing this form. In addition to signing this document, you may also be asked to sign a BIDMC General Agreement form acknowledging that you have received the BIDMC Notice of Privacy Practices.

NO EXPIRATION DATE – RIGHT TO WITHDRAW AUTHORIZATION

Your authorization for the use and disclosure of your Protected Health Information in this Study shall never expire. However, you may withdraw your authorization for the use and disclosure of your Protected Health Information at any time provided you notify the Principal Investigator in writing. If you would like to take back your authorization so that your Protected Health Information can no longer be used in this study, please send a letter notifying the Principal Investigator of your withdrawal of your authorization to Dr. Heidi Rayala, MD PhD at 330 Brookline Ave., Boston, MA. Please be aware that the investigators in this study will not be required to destroy or retrieve any of your Protected Health Information that has already been used or disclosed before the Principal Investigator receives your letter, and they are permitted to continue to use and disclose your previously collected information as necessary to complete the research.

REFUSAL TO SIGN

Your clinical treatment may not be conditioned upon whether you sign the Authorization for Research. However, if you choose not to sign this informed consent document and authorization for

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the use and disclosure of your Protected Health Information, you will not be allowed to take part in the research study.

RIGHT TO ACCESS AND COPY YOUR PHI

If you wish to review or copy your Protected Health Information as it is made part of your medical record, you may do so after the completion or termination of the study by sending a letter to the Principal Investigator requesting a copy of your Protected Health Information. You may not be allowed to inspect or copy your Protected Health Information until this study is completed or terminated.

ADDITIONAL CONTACT FOR QUESTIONS OR CONCERNS

You may contact the Human Subjects Protection Office at [617] 975-8500 in the event that you would like to obtain information or to offer input about the research study. This office is independent of the investigator or investigator's research staff and can also assist with questions relating to your rights as a participant in research, which may include questions, concerns or complaints about your participation in the study.

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THE FOLLOWING PARAGRAPHS CONTAIN SOME STANDARD INFORMATION WHICH GENERALLY APPLIES TO INDIVIDUALS PARTICIPATING IN A RESEARCH STUDY.

CONSENT FORM FOR CLINICAL RESEARCH

I have read the previous page[s] of the consent form and the investigator has explained the details of the study. I understand that I am free to ask additional questions.

If I wish additional information regarding this research and my rights as a research subject, or if I believe I have been harmed by this study, I may contact the Human Subjects Protection Office (HSPO).

I am aware that this is a research project and that unforeseen side effects may occur.

I understand that the Beth Israel Deaconess Medical Center has no formal program for compensating patients for medical injuries arising from this research. Medical treatment will be provided for injuries at the usual charge to me or to my insurer unless payment is otherwise provided for in this consent form.

I understand that participation in this study is voluntary and I may refuse to participate or may discontinue participation at any time without penalty, loss of benefits, or prejudice to the quality of care which I will receive.

I acknowledge that no guarantees have been made to me regarding the results of the treatment involved in this study, and I consent to participate in the study and have been given a copy of this form.

_____ _____

Signature of Subject or Legally Authorized Representative (Parent if the subject is a minor) — Date

_____

Relationship of Legally Authorized Representative to Subject

The subject has been given the opportunity to read this consent form and to ask questions before signing, and has been given a copy.

_____

SIGNATURE OF INVESTIGATOR/Co-Investigator DATE

_____

PRINT INVESTIGATOR'S/Co-Investigator's NAME

A signing co-investigator must be listed on the study's approved Research Staffing Form at the time of consent.

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THE FOLLOWING SECTIONS ARE NOT NEEDED FOR ALL STUDIES AND SHOULD BE UTILIZED AS INDICATED:

If the subject is able to speak and understand English but is not able to read or write

I was present during the entire oral presentation of the informed consent and witnessed the subject's agreement to participate in the study.

Signature of Witness: _____

Printed Name of Witness: _____

Date: _____

If the subject is able to understand English but is not physically able to read or write or see

I was present during the entire oral presentation of the informed consent and witnessed the subject's agreement to participate in the study.

Signature of Witness: _____

Printed Name of Witness: _____

Date: _____

If the subject is not English speaking and signed the translated Short Form in lieu of the English consent document.

As someone who understands both English and the language spoken by the subject, I interpreted, in the subject's language, the researcher's presentation of the English consent form. The subject was given the opportunity to ask questions.

Signature of Interpreter: _____

Printed name of Interpreter: _____

Date: _____