RESEARCH PROTOCOL

Cover

Title: **The Use of Focused Ultrasound and DCE K-trans Imaging to Evaluate Permeability of the Blood-Brain Barrier**

Protocol Identifying Number:

Date: 03/12/2021

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Sub-Investigatators: **Santosh Kesari, MD, PhD**

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Introduction

Treatment of intrinsic brain diseases is challenging because the blood brain barrier (BBB) limits the delivery of drugs, particulates and cellular elements such as stem cells to the central nervous system (CNS). This limitation is often circumvented with neurosurgical techniques; however, less invasive approaches may be desirable particularly for widespread or multifocal disease and when long term and repetitive administration is required.

In the past few years, several studies in animals have demonstrated that low power ultrasound pulses can temporarily disrupt the BBB with negligible deleterious effects to the brain. [1-7] In humans, with up to two hours of ultrasound exposure there is no evidence of brain injury when ultrasound is delivered with frequencies above 1.5 megahertz. [8] This phenomenon could be exploited for a noninvasive means for targeted drug delivery in the CNS. By systematically focusing the ultrasound beam at overlapping locations, one could potentially disrupt the barrier in a volume that conforms to the desired anatomical site. It could facilitate the use of therapeutic agents that are currently hampered by the BBB, such chemotherapy agents, drugs designed to treat brain neoplasia or degenerative disease and for the delivery of stem cells. Focusing of the ultrasound beam would be desirable for ensuring targeted delivery.

Two different focused systems have been developed to date. The first system employs a single ultrasound probe with a curved interface that is designed to focus the beam as an acoustic lens; this sort of device is readily available as an FDA approved device for transcranial vascular assessment. Imaging of vascular signals with the device can be used to ensure direction of the ultrasound beam while the ultrasound emissions are producing therapeutic effects. Numerous advantages characterize this simple system including the lack of need for MRI focusing, the ready availability, mobility, low cost and long safety history. Safety in therapeutic interventions has been demonstrated, but the ability to improve perfusion or to open the BBB has not been demonstrated with advanced quantitative imaging modalities. Only simple post contrast MRI scanning techniques have been used. The present study is designed to evaluate changes in perfusion and permeability` across the BBB using MRI Diffusion Contrast Enhanced imaging (DCE).

A second means of focusing ultrasound is to use a large array of multiple ultrasound probes which are pointed at a brain target. An MRI is used to focus the ultrasound by using changes in MR signal produced by tissue heating. These devices are expensive, difficult to deploy and cannot be easily adapted for repetitive therapeutic interventions. The ability to successfully target larger tissue volumes and the ability to target superficial cortical structures are all issues that need further study. Devices which are hybrids of the first and second type are now beginning to appear. Hybrid devices may offer advantages over the first type by delivering higher energies with minimal penumbra effects while avoiding cost and the recurrent MRI dependency of the second type.

With either form of focused ultrasound, there is an expected accentuation of local perfusion and potential temporary opening of the blood brain barrier with the aim is to provide better delivery of therapeutic agents including medication, particulates and cellular elements for treatment of neoplastic, inflammatory and degenerative brain diseases. The present study seeks to investigate differences in perfusion between areas treated and untreated by this modality in order to further explore its use in clinical application for the treatment of brain disease or neurodegenerative disease.

Subjects

This study will involve two separate clinical patient populations.
The diagnosis for subjects will be either low grade gliomas, or neurodegenerative disease due to various pathologies, including Parkinson's Spectrum Diseases with Dementia and Alzheimer's Spectrum Diseases. It is anticipated that ten subjects with low grade gliomas and 10 with neurodegenerative disease/memory impairment will be evaluated.
The purpose of this study is to assess the safety and efficacy of focused ultrasound for use for therapeutic application in these patient groups. Subjects will be patients already undergoing routine scans to periodically check their gliomas or neurodegenerative disease.

Glioma Patents	Neurodegenerative Patients
Inclusion Criteria: • Subjects undergoing routine, repetitive MRI scanning for monitoring low grade gliomas • 18 or older	Inclusion Criteria: • Cognitive decline with mild cognitive impairment (Clinical Dementia Rating stage 0.5) through moderate dementia CDR stages 1 and 2 • Diagnosis of Parkinson's Disease Dementia, Alzheimer's Disease, Frontal Temporal Dementia, Lewy Body Dementia, or Vascular Dementia

Exclusion Criteria: • Renal Failure defined as creatinine clearance less than 50 cc per minute • Known sensitivity to gadolinium • Claustrophobia for MRI scanners • Lack of peripheral IV site • Inability to give consent • Children, prisoners, and other vulnerable subjects	Exclusion Criteria: • Cognitive decline clearly related to an acute illness. • Patients with scalp rash or open wounds on the scalp (for example from treatment of squamous cell cancer) • Patients who would not be able to lay down without excessive movement in a calm environment sufficiently long enough to be able to achieve sleep

Methods

MRI scans will be conducted at Tower St. John's medical center and Westwood Open MRI. Subjects will be placed in a comfortable position and a DWL 2-megahertz transducer probe or a Brainsonix Pulsar 1002 transducer probe will be affixed within the temporal window by a device holder. Targeting will include reference to scalp fiducials based on the obtained MRI and Doppler waveform confirmation will be obtained because of the ability of TCD to record Doppler signal. For patients with amnestic predominant cognitive change, the target will be the mesial temporal lobe through a trans-temporal scalp window. For those with Parkinson's disease, target regions will depend on the clinical requirements; area 6 for severe motor symptoms or the frontal lobe or mesial temporal lobe for dysexecutive and amnestic syndromes, respectively.

For all subjects, the posterior cerebral artery or middle cerebral artery will be identified by standard Doppler ultrasound imaging; mechanical indices and energy parameters will be within FDA approved limits (MI of 1.9 and derated acoustic output time averaged of 720 mW per cm squared). The ultrasound treatment will last up to 2 hours or 20 minutes total time for either the DWL or Brainsonix device, respectively.

Advanced neuroimaging will be used to aid in focused ultrasound targeting. The ultrasound beam will be placed to avoid the glioma or adjacent brain so that contrast enhancement does not mistakenly signify a region of malignant transformation. MRI sequences with no contrast include: high resolution T1 weighted images, T2, Flair, SWI, ASL, and DCE perfusion. MRI

sequences with contrast include: T1, T2, Flair, SWI, and DCE perfusion. Scans will be taken one month before treatment, and post treatment.

The scans will be evaluated for any changes in perfusion. The key comparator in baseline vs. post-ultrasound will be the K trans values of DCE analysis which estimates permeability of brain vessels. ASL flow rates will be used to compare perfusion in the conditions. Statistical analysis will utilize standard Gaussian parameters for peak K trans and perfusion data (cc per minute for 100 grams of tissue) when comparing voxels within the ultrasound beam in comparison to voxels outside the beam pathway. Note that beam placement is proven by identification of a known vessel signal such as the posterior cerebral artery or middle cerebral artery.

Patients will be placed in a quiet room in a post op area of a certified outpatient surgical center monitored by the medical staff with a limited EEG montage for monitoring eye movements, muscle tone, frontal and occipital EEG for tracking sleep stages. EKG and pulse oximetry will be monitored. Standard clinical techniques used to promote sleep in the office will be used such as mild sleep deprivation, holding off on stimulants and potentially using sleep inducing medication. Slow wave sleep will be targeted. Patients will either have a) up to 2 hours of ultrasound applied with a two megahertz probe affixed with a headset with parameters set within FDA safety limits for diagnostic ultrasound, or b) 20 minutes of focused ultrasound applied with a 650 kHz probe (BrainSonix Pulsar 1002), with parameters within FDA limited for diagnostic ultrasound (I_{spta} £ 720 mW/cm^2)

Patients will be allowed to wake up after the treatment session and be discharged when fully awake and in the care of a responsible adult. Treatment will be repeated once per week for two months.

Baseline and post treatment ASL, resting BOLD and MRS will be compared for each individual. Presently, statistical comparisons can be made on an individual basis for connectivity for each brain voxel for resting BOLD and displayed as a percentile output or Z score. The region of interest selected will depend on the *(MPRAGE, T2 Flair, ASL, DCE Perfusion)* network target. For example, with amnestic predominant Alzheimer's disease we would place and ROI on the mesial temporal lobe and evaluate connectivity for output network nodes such as the anterior nucleus of the thalamus and the precuneus. Logopenic forms of Alzheimer's would utilized targeting of the temporal parietal region with an ROI in this region and connectivity analysis of frontal-parietal connections.

All patients with a neurodegenerative dementia diagnosis will have a lumbar puncture for Ab 42 and Tau proteins for Alzheimer's Spectrum. The lumbar puncture is performed once at entry. All patients will have an advanced MRI of the brain to include volume measurement of the hippocampus, ASL perfusion scans and MRS of prefrontal, precuneus, and hippocampus. On entry, patients will have. Baseline, two months (completion) testing will include the Quick Dementia Rating System (QDRS) for staging and the following battery of tests:

- The Repeatable Battery for Assessment of Neuropsychological Status (RBANS),

- Standardized 25-foot timed gait test
- The Nine Hole Pegboard Test
- Montreal Cognitive Assessment Test versions 1,2,3 (MOCA),
- Brain imaging will be repeated at completion that will include an anatomical scan (MPRAGE), ASL and BOLD and MRS in the targeted network.

CSF studies have demonstrated good sensitivity and specificity for MCI and dementia of the Alzheimer's type (ref 5). MRI volumetrics, perfusion scans and MR spectroscopy have shown to be of excellent discriminating value among AD, PDD/DLB and FTLD subgroups and is responsive to change as patient's progress from MCI to dementia.

This is a safety and efficacy study. There is no expectation regarding hypothesized efficacy. The hypothesized effects would be any changes made in the K trans post focused ultrasound compared to normal, untreated tissues.

Risk and Benefit Assessment

Potential Risks

The risk/benefit profile is specific to the study protocol, not to the disease. Therefore, the profiles of low-grade gliomas and all 5 of the Neurodegenerative Dementia Diagnoses.

The following are potential safety concerns associated with interventions made during the study:

1. The administration of gadolinium contrast: Very low risk of a progressive fibrosis syndrome with those subjects without renal failure. This is characterized by thickening and painful changes in skin (10-11).

Protection against risks:

The scans and the procedure will be done at Tower St. John's medical center, a medical facility equipped to handle any adverse reactions to contrast agents. Medical personnel, including the principal investigator, Dr. Jordan, will be on site in case of an emergency. Patients will be evaluated by the principal investigator both before and after their scan. Any side effects will be tracked and monitored. The only anticipated side effects are itching, dizziness, headache, or possible neurological problems. If there are any high-grade adverse effects the study will be discontinued. Patients will follow up with their treating physician. Any side effects will be reported directly after the scans by Dr. Jordan. All subjects will be screened for renal function to protect against reaction to the gadolinium contrast. This screening will require standard tests for renal function.

Potential Benefits

This study seeks to investigate the efficacy of focused ultrasound in opening the blood brain barrier. This physiological effect would have significant clinical applications. The ability to open the blood brain barrier has the potential to revolutionize the delivery of therapeutic agents to the brain, allowing for more localized and efficient delivery. Furthermore, this could allow clinicians to more readily treat neoplastic, inflammatory, and degenerative brain diseases. There are no immediate benefits for patients who choose to participate; however, the information gained from this study will contribute to the research base and help patients in similar situations in the future.

Data Analysis

Statistical analysis will use standard Gaussian parameters for peak K trans and perfusion rate (1cc per minute for 100 grams of tissue). Tissue within the ultrasound beam will be compared to tissue outside of the ultrasound beam.

Data Storage and Confidentiality

Data will be stored in compliance with HIPAA regulations. All information will be stored within medical facilities. All physical and electronic copies of subject data will be locked up or password protected to ensure patient confidentiality. Information will not be released without written permission of the participant, except as necessary for monitoring by IRB, the FDA, the NIA, and the OHRP.

Participant Rights and Confidentiality

- Institutional Review Board (IRB) Review
- Informed Consent Forms
- Participant Confidentiality
- Study Discontinuation

The IRB, the NIA, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research participants are protected may discontinue the study at any time.

Subject Identification, Recruitment and Consent

Method of Identification and Consent

Patient recruitment will be done through routine medical practice. Subjects will be identified based on their diagnosis, only subjects low grade gliomas will be included. The diagnosis will be made by one of the investigators on the study, Dr. Jordan, Dr. Kesari, or Dr. Peddi. Only subjects with low grade gliomas or a diagnosis of neurodegenerative dementias will be asked to be in the study. If the subject agrees to participate in the study, he or she will then be presented with the

consent forms. Consent will be obtained prior to the beginning of the MRI scan and IV infusion. Once the consent forms have been read, the subject has been able to ask their questions, and the subject signs the form, they will then be an active participant in the study.

Process of Consent

Consent will be obtained prior to any interventions. The principal investigator, all sub-investigators, and research coordinators will be authorized to obtain consent from the patient. Subjects will be taken to a private room in order to obtain consent. They will be informed the purpose of the study. Subjects may take as long as they need to review the consent documents. All subjects have the right to ask any questions that they have regarding the nature of the research or the interventions. It is required that the subject speaks the English language to ensure they comprehend the consent process. No coercion of any kind is permitted, the choice to participate must be entirely the patient's. The patient has the right to have a witness in the room during the consenting process. They also have the right to decline participation or leave the study at any time.

Subject Capacity

Subjects participating in this study must have the capacity to give consent. Any cognitive impairments, inhibited capacity, or inability to comprehend the consent in any way will be prohibited. Capacity to give informed consent will be determined by investigators and research coordinators.

Debriefing procedures

No information is withheld for the present study; therefore, debriefing is unnecessary. However, if the patient has questions at any point throughout the study, they have the right to ask. This study is open label and unblinded.

Documentation of Consent

Consent will be obtained from the patient prior to the MRI. This will be done in private as stated before. Once the subject has consented, a copy will be kept of the signed consent forms. These forms will be kept physically and electronically by the research coordinators. Electronic copies will be scanned on to computers that are username and password protected and are equipped with a firewall. These computers will be on site of medical practices only and accessible only to staff. The physical copy will be stored in a locked file cabinet. This will only be accessible by staff. Subjects will be given a copy of any consent forms they sign. All documentation will be HIPAA compliant as is standard medical practice.

Costs to Subject

Apart from the charges of the MRI scan, which the patients are already paying, subjects will pay no additional cost to participate in the study. There will be no costs to the subject for the focused ultrasound, the IV infusion, or for the doctor's time. The only charge subjects will be responsible for is the MRI itself.

Payment for Participation

There will be no compensation of any form given for participation in the present study. This includes financial reimbursement of any kind, academic credit, or any other kind of reimbursement. If the patient chooses to drop out of the study at any time, he or she has the right to do so but will not be reimbursed for the time they spent in the study.

References

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ACKNOWLEDGMENT OF CONSENT TO PARTICIPATE IN THE NEUROLOGICAL ASSOCIATES - THE INTERVENTIONAL GROUP STUDY ON THE USE OF FOCUSED ULTRASOUND AND DCE K-TRANS TO EVALUATE PERMEABILITY OF THE BLOOD-BRAIN BARRIER.

I,_____, hereby request and authorize:

Sheldon Jordan, M.D., F.A.A.N.

Neurological Associates - The Interventional Group,
Tower Saint John's Imaging,

To perform the following procedure:
Magnetic resonance imaging (MRI)
Focused Ultrasound

PURPOSE OF THIS RESEARCH STUDY

I understand the purpose of this procedure is to examine the effects of focused ultrasound for altering brain perfusion and the blood brain barrier.
Recent medical studies have shown that the use of focused ultrasound allows for temporary disruption of the blood brain barrier. This has implications for therapeutic purposes in the treatment of various brain diseases. The current study seeks to explore these effects.
You are being asked to be included in this study since you have been diagnosed with a low-grade glioma or degenerative dementias. It is appropriate for subjects to ask any questions about this form and you may even take this form home for consideration before signing. To determine whether you are an appropriate candidate for this study we will ask you to disclose all of your medical history and conditions. If you do not completely disclose your medical history and conditions and comply strictly with the protocol, you could be exposed to serious medical risks including disability and death. You are not a candidate for this study if you have any of the following: Renal Failure, known sensitivity to gadolinium, claustrophobia for MRI scanners, lack of peripheral IV site, or if you are under the age of 18.

POSSIBLE BENEFITS

The potential benefit of focused ultrasound infusion is more localized delivery of therapeutic agents for brain diseases. There are no immediate benefits for patients who choose to participate; however, the information gained from this study will contribute to the research base and help patients in similar situations in the future. We do not know how each individual will respond to focused ultrasound, MRI scans, or contrast agents, but precautions are taken to ensure maximum safety for all patients.

POSSIBLE RISKS OR DISCOMFORT

The ultrasound examination has no clinically apparent side effects. However, the administration of gadolinium contrast has a very low risk of a progressive fibrosis syndrome with those patients without renal failure; this is characterized by thickening and painful changes in skin.

Other possible risks could include potentially harmful reactions to resuscitative medications or measures (chest compressions, electrical shock, CPR in general, and/or call 911) in the event that a life-threatening reaction is encountered and requires treatment.

AVAILABLE TREATMENT ALTERNATIVES

This research explores the efficacy of a new modality and therefore would have no impact upon treatment outcomes. If patients choose not to participate it would have no bearing on their treatment protocol and they would continue with their normal course of treatment.

FINANCIAL CONSIDERATIONS

I have been informed that my focused ultrasound will be performed at no additional cost. As a patient, there will be no cost for the focused ultrasound, or the doctor's time. The only cost I am responsible for is that of the MRI scan.

By participating in this study, I will not be entitled to any remuneration from any patents or later company profits.

I authorize the doctors acting as investigators for this study as listed above to employ assistants, nurses, physicians, radiologists, and/or anesthesiologists, or technologists necessary for the procedure and approve their participation.

My participation in this research protocol is voluntary and may be withdrawn at any time without penalty. My participation in this may also be withdrawn at any time by any of the investigators for any reason without my consent.

I authorize The Neurological Associates - The Interventional Group and assistants, photographers and technicians to take photographs or video recordings necessary before, during and after.

*****Please initial appropriate line: I Permit _____I do NOT Permit____** such photographs or video recordings and any information relating to my case to be published in professional journals and medical books or to be used for any other purpose that Neurological Associates - The Interventional Group may deem appropriate without any further consent, authorization or release by me.

I am willing to discuss my experience with other patients of Neurological Associates - The Interventional Group. **YES_____ NO _____**

You must be advised that in case of emergency we will provide resuscitative procedures. **I agree_____ I do NOT agree _____**

For women: MRI presents unknown risks to women who are pregnant or who may become pregnant after deployment. There are also unknown risks to an embryo or fetus. Standard procedures are in place at Tower Saint John Imaging Center in order to protect both pregnant women and fetuses. Therefore, I waive any claim I may have against The Neurological Associates - The Interventional Group should I unexpectedly find myself to be/have been pregnant during my procedure. I also understand that I have the right to request a pregnancy test after signing this informed consent.
***** Please initial ___YES_____ NO ___**

By signing this consent, I acknowledge that I (1) read this form (or it was read to me) carefully (2) asked any question that I wished, (3) received satisfactory answers to my questions and requests for additional information, (4) will disclose my medical history and conditions truthfully and completely to the practice, and (5) will inform the practice promptly of any change in my health or symptoms or any complication of treatment. (6) Voluntarily agree to participate in the research protocol.
I will receive a copy of this signed and dated consent.

_____ _____
Signature of Patient or Legal Guardian Date

_____
Printed Name of Patient or Legal Guardian

_____
Witness' Signature Date

_____
Signature of person giving informed consent

For any questions about the following:

- Questions about the research
- Questions about research-related injury or illness.
- Questions about one's rights as research subjects

Contact Dr. Sheldon Jordan, MD, at 310-829-5968.

AUTHORIZATION TO USE AND DISCLOSE PROTECTED HEALTH INFORMATION FOR RESEARCH PURPOSES

THE NEUROLOGICAL ASSOCIATES - THE INTERVENTIONAL GROUP.

Principal Investigator:
Sheldon Jordan, M.D., F.A.A.N.

Sub Investigators:
Dr. Santosh Kesari
Dr. Srinivas Peddi

STUDY TITLE AND NUMBER: THE USE OF FOCUSED ULTRASOUND AND DCE K-TRANS TO EVALUATE PERMEABILITY OF THE BLOOD-BRAIN BARRIER.

Research, Privacy, and the new Health Insurance Portability and Accountability Act (HIPAA)

1. What is the purpose of this form?
We would like to use your health information for research. This information includes data that identifies you during the process of data collection. The
Federal Health Insurance Portability and Accountability Act (HIPAA) of 1996 require your approval to use health information about you that identifies individuals. This approval is called an Authorization.
By signing this Authorization form, you are giving permission for the use of your protected health information for research purposes. This information may include data that identifies you. Please carefully review the information below. If you agree that we can use your protected health information, you must sign and date this form to give your approval.

2. What protected health information do the researchers want to use? The researchers want to copy and use the portions of your medical record that will be needed for their research. If you participate in this research study, information that will be used and/or released may include the following:

We will use your information from your medical records, results of laboratory tests and case report forms and both clinical and research observations made while you take part in the research. Clinical information collected will include any new diagnoses, reported symptoms, changes in body appearance, how well you feel physically and emotionally, what medications you are prescribed and how many times you have missed taking your prescribed study medication, and any problems you may be having that are related to taking your study medication. Blood may be collected at each study visit and the results of those tests will also be recorded.

3. *Why do the researchers want my protected health information?*

In enacting HIPAA, Congress mandated the establishment of Federal standards for the privacy of individually identifiable health information. The Privacy Rule establishes safeguards to protect the confidentiality of medical information and provides guidelines for research organizations such as Kessler Foundation Research Center to use or disclose protected health information for purposes preparatory to research such as to aid study recruitment. We believe that the protection of identified medical information will facilitate medical research because research participants know that their information is protected in accordance with the Privacy Rule.

4. *Who may see your protected health information for this research study?*

Your health information may be shared with people and researchers at this institution and associates of the sponsor(s), university, clinic or hospital who help with the research. We may share this information with others who are in charge of the research and/or who pay for or work with us on the research or those who make sure that we do this research properly. This authorization form will explain how your protected medical information will be used and shared (disclosed) in this research study.

To meet regulations or for reasons related to this study, the study team may share a copy of this approval form and records that identify you with the following people:

- The Institutional Review Board - a committee that reviews research studies for the protection of the people who participate in research.

5. *What happens if I sign this Authorization?*

If you agree to give approval to use and share your protected information as described in this form, your authorization will not expire unless you cancel it. The information collected during your participation for this study will be kept indefinitely. By signing this approval form, you give us permission to use and share your protected health information

6. *What happens if I do not sign this approval form?*

If you do not sign this approval form, you will not be able to take part in the research study for which you are being considered.

7. *If I sign this form, will I automatically be entered into the research study?*

No, you cannot be entered into any research study without further discussion and a separate consent form. After discussion, you may decide to take part in the research study. At that time, you will be asked to sign a specific research approval (Informed Consent) form.

8. ***What happens if I want to remove my approval?***

You can change your mind at any time and remove your approval to allow your protected health information to be used in the research. If this happens, you must remove your approval in writing. Beginning on the date you remove your approval, no new protected health information will be used for research. However, researchers may continue to use the health information that was provided before you withdrew your approval.

If after signing this form, you want to remove your approval, please contact the person(s) below. He/she will make sure your written request to remove your approval is processed correctly.

Sheldon Jordan, M.D., F.A.A.N.
Tel. 310-829-5968 Fax. 310-453-3685

Members of the study team, including Dr. Kesari, and Dr. Peddi.

FDA (United States Food and Drug Administration) - the government agency that reviews all research information for approval of new drugs and treatments for the public.

You have the right to look at your study information at the study doctor's office and to ask (in writing) for corrections of any of your information that is wrong.

We will make every effort to keep information we learn about you private. However, research involves gathering, recording, and transferring information that needs to be verified and other people may need to see the information (these others are listed on this form). Some of these people may share your health information with someone else. If they do, the same laws that the hospital, clinic or institution must obey to protect your health information may not apply to these other people or institutions.

9. ***How long will these approvals last?***

If you agree by signing this form that researchers can use your protected health information, this approval has no expiration date. However, as stated above, you can change your mind and remove your approval at any time. Questions should be directed to the research staff person who is reviewing this form with you. You can also call the Neurological Associates - The Interventional Group office manager at (310) 829-5968 ex: 246, or research study coordinators at (310) 829-5968 ex: 214.

SIGNATURE PAGE

This form does not replace the Informed Consent to participate in research. It provides additional information related to the use and disclosure of your protected health information. Your signature means that you are giving approval (authorization) for the use and disclosure of your protected health information for research purposes, as described in this form. You will be given a copy of this form to keep.

_____ _____

Signature of Research Participant **Date**

_____

Printed Name of Research Participant

_____

Signature of Investigator Obtaining Approval **Date**

_____

Printed Name of Investigator