TITLE

Elastography in Thyroid Nodule Evaluation

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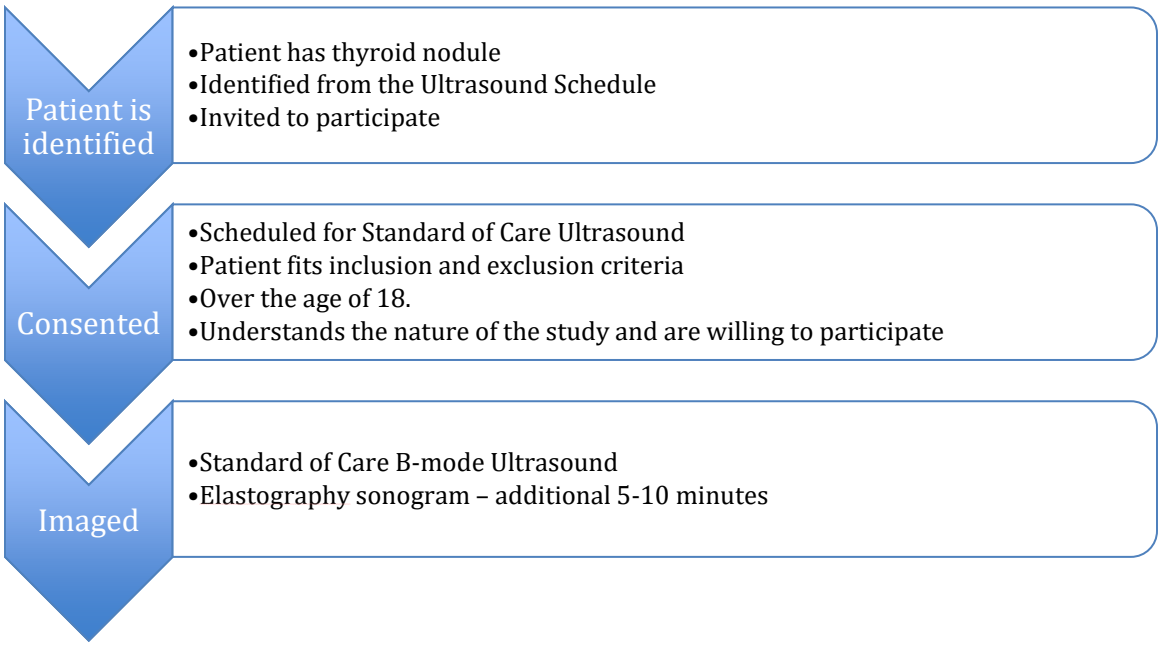
Schema


Patient is identified
•Patient has thyroid nodule
•Identified from the Ultrasound Schedule
•Invited to participate
Consented
•Scheduled for Standard of Care Ultrasound
•Patient fits inclusion and exclusion criteria
•Over the age of 18.
•Understands the nature of the study and are willing to participate
Imaged
•Standard of Care B-mode Ultrasound
•Elastography sonogram – additional 5-10 minutes

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

CBC	Complete blood count
CI	Confidence interval
CMAX	Maximum concentration of drug
CNS	Central nervous system
CRF	Case report/Record form
CR	Complete response
CSM	Conventional Staging Method
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ECOG Performance Status	Easter Cooperative Oncology Group Performance Status
EFS	Event Free Survival
FDG	Fluorodeoxyglucose
GI	Gastrointestinal
Hgb	Hemoglobin
HIV	Human Immunodeficiency Virus
HPF	High-power field
HTN	Hypertensions
IPI	International Prognostic Index
IRB	Institutional Review Board
IV	Intravenous
LLN	Lower limit of normal
NHL	Non-Hodgkin's Lymphoma
NPV	Negative Predictive Value
OS	Overall survival
PET/CT	Positron emission tomography – computed tomography
PLT	Platelet
PD	Progressive diseased
PPV	Positive Predictive Value
PFS	Progression free survival
PR	Partial response
QD	Once daily
RECIST	Response evaluation criteria in solid tumors
RM	Residual Mass
ROC	Receiver-Operative-Characteristic
RR	Response rate
SAE	Serious adverse event
SD	Stable disease
SUV	Standard Uptake Value
TTP	Time to progression
ULN	Upper limit of normal
UNK	Unknown

1. OBJECTIVES

1.1. Primary Objective

The purpose of this study is to determine the utility of ultrasound elastography in evaluation of thyroid nodules. Elastography is a non-invasive method in which stiffness or strain images of soft tissues are used to characterize a nodule or mass lesions. Tissue that is more stiff is thought to have a greater risk of malignancy.

1.2. Secondary Objectives

No secondary objective.

2. BACKGROUND

2.1. Study Disease

Patients with thyroid nodules will be studied.

2.2. Study Agent/Device/Imaging procedure

Patients are not given a treatment or imaging agent. They are having a procedure - an Elastography Ultrasound (experimental) as well as a standard of care ultrasound.

2.3. Clinicaltrials.gov

This investigation does not require an Investigational New Drug application (IND).

2.4. Rationale

Thyroid nodules are extremely common, affecting nearly half of the adult population. Although extremely common, a minority, between 1.5 – 10% of thyroid nodules, are malignant. [1] Differentiation between benign and malignant nodules however, based on physical examination and ultrasound imaging is very difficult and generally is referred for invasive percutaneous biopsy or surgical excision for definitive diagnosis.

Because of the very common occurrence of thyroid nodules in the general public, there is a great need for a noninvasive means of stratifying those who are at greater risk of malignancy from those who are more likely to harbor a benign nodule for which no treatment is necessary.

Recent studies have examined elastography in thyroid nodules with findings of high sensitivity and good specificity. [2] Other investigators have looked at elastography in evaluation of other [3] [4] It is thought that lesions that are stiffer are more likely to represent malignancy or other pathology than benign or normal tissue which tend to be more softer.

Elastography is a noninvasive ultrasound technology which can evaluate the stiffness of a lesion compared to the background tissue. There are two major methods of measuring stiffness: strain imaging, and shear wave velocity measurement. In strain imaging, ultrasound maps the relative tissue deformity by extrinsic compression and provides a color map. Greater deformation with pressure corresponds to more elastic tissue and less deformation corresponds to stiffer tissue. In the second method, shear waves are sent through a given volume of tissue and the speed of the shear wave propagation is measured. Since stiffer tissues have higher shear wave velocities, this can be correlated with tissue

stiffness to provide a more quantative measurement. Velocities can then be used to calculate Young modulus in kPa. [5]

Most shear wave elastography measurements currently available use a single point measurement; however, a new 2-D shear wave elastography measurement technique will be used in our study to measure stiffness of thyroid nodules. This will allow sampling of a larger area of a nodule instead of just one point, which may be more representative of the nodule's overall stiffness.

2.5. Preliminary results

Preliminary results show that the stiffness or elastography values of malignant nodules tend to be greater than benign thyroid nodules.

2.6. Study Design

- Single Group
- There will be one intervention arm
- The study will be open: no masking is used
- The study is not randomized

3. PARTICIPANT SELECTION AND ENROLLMENT PROCEDURES

3.1. Inclusion Criteria

3.1.1. Age greater than or equal to 18 years.

3.1.2. Presence of a thyroid nodule that is amenable to ultrasound guided fine needle aspiration.

3.2. Exclusion Criteria

3.2.1. Patients younger than 18

3.2.2. Patients who are unable to lie supine for a biopsy.

3.2.3. Pregnant patients

3.3. Informed Consent Process

All participants must be provided a consent form describing the study with sufficient information for participants to make an informed decision regarding their participation. Participants must sign the IRB approved informed consent prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent

document. The original signed copy of the consent document must be retained in the medical record or research file.

3.4. Randomization Procedures
This is an open label study, therefore patients will not be randomized.

3.5. Study Timeline

3.5.1. Primary Completion:
The study will reach primary completion 36 months from the time the study opens to accrual.

3.6. Study Completion:
The study will reach study completion 36 months from the time the study opens to accrual.

4. IMAGING AGENT/DEVICE/PROCEDURE INFORMATION

4.1. Name of Study Agent/Device/Imaging Procedure

No imaging agent will be used in this study.

- The examination will consist of an ultrasound elastography assessment in which an ultrasound machine is used to evaluate elastography measurements of a thyroid nodule.
- Each patient will undergo one ultrasound elastography assessment of the thyroid prior to either fine needle aspiration or surgical resection of the thyroid nodule (invasive procedure is not part of the study)
- No radiation will be used for this examination. Ultrasound is an imaging modality that uses sound waves, not radiation in imaging.
- Ultrasound machines are FDA approved.

5. STUDY PROCEDURES

5.1 Criteria for Removal from Study
After patient has ultrasound elastography of the thyroid nodule, they will have completed the study. If the patient cannot lie still in supine position then they will be removed from the study.

5.2 Alternatives
Alternative is to not participate in the study and continue with planned standard of care ultrasound and/or fine needle aspiration of thyroid nodule.

6. STUDY CALENDAR

	Pre-Study	Procedure- post consent
Investigational Agent		

Informed consent	X	
Radiologic evaluation (ultrasound)		X

7. ADVERSE EVENTS AND REPORTING PROCEDURES

7.1. Potential Adverse Events

There are no known side effects or adverse events from elastography. However, if any are detected, they will be reported.

7.2. Adverse Event Reporting

No adverse events are expected to occur in this study.

Adverse events will be graded according to CTCAE v4.0. Both Serious and Non-Serious Adverse Events will be clearly noted in source documentation and listed on study specific Case Report Forms (CRFs). The Protocol Director (PD) or designee will assess each Adverse Event (AE) to determine whether it is unexpected according to the Informed Consent, Protocol Document, or Investigator's Brochures, and related to the investigation. All Serious Adverse Events (SAEs) will be tracked until resolution and 30 days after the last dose of the study treatment.

8. REGULATORY CONSIDERATIONS

8.1. Institutional Review of Protocol

The protocol, the proposed informed consent and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the Stanford IRB and Scientific Review Committee (SRC). Any changes made to the protocol will be submitted as a modification and will be approved by the IRB and SRC prior to implementation. The Protocol Director will disseminate the protocol amendment information to all participating investigators.

8.2. Data Management Plan

Data will be stored in Oncore and REDCap. Other data will be stored on a password protected and encrypted computer or on a HIPAA compliant server through Stanford, BOX.

8.3. Data and Safety Monitoring Plan

During the clinical investigation, the Protocol Director will evaluate the progress of the trial, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, and other factors that can affect study outcome.

The Stanford Cancer Institute Data and Safety Monitoring Committee (DSMC) will audit study related activities at least annually in accordance with the DSMC SOP to determine whether the study has been conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). This may include review of regulatory binders, case report forms, eligibility checklists, and source documents. In addition, the DSMC will regularly review serious adverse events and protocol deviations associated with the research to ensure the protection of human subjects. Results of DSMC audits will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as needed.

9. MEASUREMENTS

9.1. Primary and Secondary Outcome measures

Elastography shear wave velocity measurements of thyroid nodules will be compared to fine needle aspiration biopsy results or surgical pathologic specimens, if available.
No secondary outcome measurements will be made.

9.2. Measurement methods

Elastography shear wave velocity measurements of thyroid nodules (which are calculated by the ultrasound machine at the time of the elastography measurements) will be compared to fine needle aspiration biopsy results or surgical pathologic specimens, if applicable.

9.3. Measurement Time Points

Elastography shear wave velocity measurements of thyroid nodules will be compared to fine needle aspiration biopsy results or surgical pathologic specimens, if applicable. No follow-up imaging or assessment will be required.

9.4. Response Review

No response review is planned.

9.5. Secondary Outcome

There is no secondary outcome.

10. STATISTICAL CONSIDERATIONS

10.1. Statistical Design

This is a prospective single arm blinded study in which patients who come for biopsy or surgical resection will be analyzed with elastography prior to biopsy or surgical resection. A sample size of 10 vs 43 provide 80% power for detecting a difference of 0.84 m/sec at the significance level of 0.05 based on Wilcoxon rank sum test assuming that the sound velocity for benign (and malignant nodules) follows a Gaussian distribution). The standard deviation is 0.79 meters/second based on the observed standard deviation from our pilot data.

We propose to use Wilcoxon rank sum test for its robustness in cases where the velocity does not follow the Gaussian distribution. Even if the Gaussian assumption is true, the Wilcoxon rank sum test is almost as powerful as the parametric t-test.

Randomization

Patients are not randomized in this study.

10.2. Interim analyses

There will not be a statistical stopping rule. Every three months, the data collected will be analyzed and a record of the monitoring activities wil be maintained by the study team.

10.3. Descriptive Statistics and Exploratory Data Analysis

The distribution of the elastography measurements will be summarized by mean and standard deviation. If the distribution is highly non-Gaussian, then median and other quantiles will be provided as well. The summaries will be provided by malignancy status.

10.4. Primary Analysis

The primary analysis will be a comparison of tissue stiffness measured by the sound

velocity between malignant and benign nodules. To this end, the two-sided two sample Wilcoxon rank sum test will be used and the statistical significance level is 0.05.

10.4.1. Analysis Population

Analysis population is 53 patients expected to consist of 10 cancer patients and 43 non-cancer patients.

10.4.2. Analysis Plan

Appropriate summary statistics will be provided for the sound velocity by the malignancy status. two-sided two sample Wilcoxon rank sum test will be used to compare of tissue stiffness measured by the sound velocity between malignant and benign nodules

10.5. Secondary Analysis

NA.

10.5.1. Analysis Population

NA

10.5.2. Analysis Plan

NA

10.6. Sample Size

53 patients

10.7. Accrual estimates

We expect to accrue 53 patients over 3 years.

10.8. Criteria for future studies

If current study yields promising results, a larger study may be performed with utilization of other types of ultrasound elastography measurements. Since elastography measurements may vary between ultrasound machines as well as different elastography techniques, it will be important to understand which technique yields the most reliable and consistent results.

11. REFERENCES

1. Hegedus L. Clinical practice. The thyroid nodule. N Engl J Med 2004;351:1764-1771
2. Bojunga J, Herrmann E, Meyer G, Weber S, Zeuzem S, Friedrich- Rust M. Real-time elastography for the differentiation of benign and malignant thyroid nodules: a meta-analysis. Thyroid;20:1145-1150
3. Cosgrove DO, Berg WA, Dore CJ, et al. Shear wave elastography for breast masses is highly reproducible. Eur Radiol. 2012 May;22(5):1023-32

4. Bhatia KS, Cho CC, Tong CS, Lee YY, Yuen EH, Ahuja AT. Shear wave elastography of focal salivary gland lesions: preliminary experience in a routine head and neck US clinic. Eur Radiol 2012 May;22(5):957-65

5. **Kamaya** A, Machtaler S, Safari Sanjani S, Nikoozadeh A, Graham Sommer F, Pierre Khuri-Yakub BT, Willmann JK, Desser TS. New technologies in clinical ultrasound. Semin Roentgenol. 2013 Jul;48(3):214-23

Appendix A: Inclusion/Exclusion Criteria Checklist

Inclusion Criteria (From IRB approved protocol)	**Yes**	**No**	**Supporting Documentation***
1. Patient is ≥ 18 years old at the time of the participation	☐	☐	
2. Presence of a thyroid nodule	☐	☐	
Exclusion Criteria (From IRB approved protocol)			
1. Patients younger than 18	☐	☐	
2. Patients who are unable to lie supine for a biopsy	☐	☐	
3. Pregnant Patients	☐	☐	

IV. Statement of Eligibility

This subject is [☐ **eligible** / ☐ **ineligible**] for participation in the study.

Signature:	Date:
Printed Name:	

Signature:	Date:
Printed Name:	
Signature:	Date:
Printed Name:	

Are you participating in any other research studies? _____ Yes _____No

PURPOSE OF RESEARCH

You are invited to participate in a research study of ultrasound elastography of thyroid nodules. We hope to learn whether elastography is an effective technique for imaging nodules in the thyroid. You were selected as a possible participant in this study because you have a thyroid nodule that will be biopsied.

This research study is looking for 50 patients with thyroid nodules being seen at Stanford University Hospital Department of Radiology for a thyroid biopsy. Stanford University expects to enroll 50 research study participants.

VOLUNTARY PARTICIPATION

Your participation in this study is entirely voluntary. Your decision not to participate will not have any negative effect on you or your medical care. If you wish to participate in this study, you must sign this form. You can decide to participate now, but withdraw your consent later and stop being in the study without any loss of benefits or medical care to which you are entitled.

If you decide to terminate your participation in this study, you should notify Dr. Aya Kamaya [redacted]

DURATION OF STUDY INVOLVEMENT

Your participation in this research study is expected to take approximately 15 minutes, with screening of each participant taking approximately 5 minutes, and elastography imaging taking less than 10 minutes. The duration of the entire study is expected to take approximately three years, including time for data analysis.

PROCEDURES

If you choose to participate, Dr. Kamaya or a designated representative from her research study staff will describe the procedure to you before performing an ultrasound elastography study of your thyroid.

Though ultrasound has been used routinely in hospitals for decades, we are studying the effectiveness of ultrasound elastography, which is an experimental imaging study. The ultrasound elastography imaging study will take less than 10 minutes, and will involve using a special ultrasound machine with elastography capabilities. Elastography measurements will be obtained, which measures the degree of compressibility of the thyroid nodule compared to background thyroid tissue. There is no ionizing radiation involved with elastography and there is no known side effect of elastography imaging.

IF YOU FEEL DISCOMFORT AT ANY TIME, NOTIFY THE OPERATOR AND YOU CAN DISCONTINUE THE EXAM AT ANY TIME.

PARTICIPANT RESPONSIBILITIES

As a participant, your responsibilities include:

- Follow the instructions of the Protocol Director and study staff.
- Ask questions as you think of them.
- Tell the Protocol Director or research staff if you change your mind about staying in the study.

WITHDRAWAL FROM STUDY

If you first agree to participate and then you change your mind, you are free to withdraw your consent and discontinue your participation at any time. Your decision will not affect your ability to receive medical care for your disease and you will not lose any benefits to which you would otherwise be entitled. You may withdraw at any time by verbally indicating your desire to withdraw.

If you decide to withdraw your consent to participate in this study, you should notify Dr. Aya Kamaya at [redacted].

The Protocol Director may also withdraw you from the study without your consent for one or more of the following reasons:

- Failure to follow the instructions of the Protocol Director and study staff;
- The study is cancelled;
- Other administrative reasons;
- Unanticipated circumstances.

POSSIBLE RISKS, DISCOMFORTS, AND INCONVENIENCES

- There are risks, discomforts, and inconveniences associated with any research study. These deserve careful thought. You should talk with the Protocol Director if you have any questions.

- *You will be expected to lie still during the ultrasound elastography study for approximately 10 minutes, which may be uncomfortable.*

POTENTIAL BENEFITS

This study may result in the acquisition of important knowledge that may benefit future patient management; however, **we cannot and do not guarantee or promise that you will receive any benefits from this study.**

ALTERNATIVES

The alternative to voluntary participation is not to participate.

PARTICIPANT'S RIGHTS

You should not feel obligated to agree to participate. Your questions should be answered clearly and to your satisfaction. If you decide not to participate, tell the Protocol Director.

You will be told of any important new information that is learned during the course of this research study, which might affect your condition or your willingness to continue participation in this study.

CONFIDENTIALITY

Your identity will be kept as confidential as possible as required by law. Except as required by law, you will not be identified by name, social security number, address, telephone number, or any other direct personal identifier. Your research records may be disclosed outside of Stanford, but in this case, you will be identified only by a unique code number. Information about the code will be kept in a secure location and access limited to research study personnel.

The results of this research study may be presented at scientific or medical meetings, or published in scientific journals. However, your identity will not be disclosed**.**

Patient information may be provided to Federal and other regulatory agencies as required. The Food and Drug Administration (FDA), for example, may inspect research records and learn your identity if this study falls within its jurisdiction.

ClinicalTrials.gov

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

Authorization to Use Your Health Information for Research Purposes

Because information about you and your health is personal and private, it generally cannot be used in this research study without your written authorization. If you sign this form, it will provide that authorization. The form is intended to inform you about how your health information will be used or disclosed in the study. Your information will only be used in accordance with this authorization form and the informed consent form and as required or allowed by law. Please read it carefully before signing it.

What is the purpose of this research study and how will my health information be utilized in the study?
The purpose of your participation in this study is the evaluation and optimization of ultrasound elastography techniques for thyroid nodule imaging. Technical evaluation of your scans will allow determination of the best techniques for ultrasound elastography imaging of thyroid nodules.

Do I have to sign this authorization form?
You do not have to sign this authorization form. But if you do not, you will not be able to participate in this research study. Signing the form is not a condition for receiving any medical care outside the study.

If I sign, can I revoke it or withdraw from the research later?
If you decide to participate, you are free to withdraw your authorization regarding the use and disclosure of your health information (and to discontinue any other participation in the study) at any time. After any revocation, your health information will no longer be used or disclosed in the study, except to the extent that the law allows us to continue using your information (e.g., necessary to maintain integrity of research). If you wish to revoke your authorization for the research use or disclosure of your health information in this study, you must notify Dr. Kamaya in writing at 300 Pasteur Drive, H1307, Stanford, CA 94305-5105.

What Personal Information Will Be Used or Disclosed?
Your health information related to this study, may be used or disclosed in connection with this research study, including, but not limited to your name, medical record number, age, imaging information and any laboratory or clinical information related to the thyroid nodule.

Who May Use or Disclose the Information?
The following parties are authorized to use and/or disclose your health information in connection with this research study:

- The Protocol Director, Dr. Aya Kamaya
- The Stanford University Administrative Panel on Human Subjects in Medical Research and any other unit of Stanford University as necessary
- Research Staff

Who May Receive or Use the Information?
The parties listed in the preceding paragraph may disclose your health information to the following persons and organizations for their use in connection with this research study:

- The Office for Human Research Protections in the U.S. Department of Health and Human Services
- Siemens Inc.
- The Food and Drug Administration

Your information may be re-disclosed by the recipients described above, if they are not required by law to protect the privacy of the information.

When will my authorization expire?
Your authorization for the use and/or disclosure of your health information will expire on December 31, 2058 or when the research project ends, whichever is earlier.

_____ _____
Signature of Adult Participant Date & Time

_____
Print Name of Adult Participant

FINANCIAL CONSIDERATIONS

Payment: You will not be paid to participate in this research study.

Costs: There is no cost to you for participating in this study.

Sponsor: Siemens Medical Solutions USA, Inc.is providing financial support and/or material for this study.

COMPENSATION for Research-Related Injury

All forms of medical diagnosis and treatment – whether routine or experimental – involve some risk of injury. In spite of all precautions, you might develop medical complications from participating in this study. If such complications arise, the Protocol Director and the research study staff will assist you in obtaining appropriate medical treatment. In the event that you have an injury or illness that is directly caused by your participation in this study, reimbursement for all related costs of care first will be sought from your insurer, managed care plan, or other benefits program. **You will be responsible for any associated co-payments or deductibles as required by your insurance.**

If costs of care related to such an injury are not covered by your insurer, managed care plan or other benefits program, you may be responsible for these costs. If you are unable to pay for such costs, the Protocol Director will assist you in applying for supplemental benefits and explain how to apply for patient financial assistance from the hospital.

You do not waive any liability rights for personal injury by signing this form.

CONTACT INFORMATION

Questions, Concerns, or Complaints: If you have any questions, concerns or complaints about this research study, its procedures, risks and benefits, or alternative courses of treatment, you should ask the Protocol Director, Dr. Kamaya. You may contact her now or later at [redacted]. You should also contact her at any time if you feel you have been hurt by being a part of this study.

Independent Contact: If you are not satisfied with how this study is being conducted, or if you have any concerns, complaints, or general questions about the research or your rights as a participant, please contact the Stanford Institutional Review Board (IRB) to speak to someone independent of the research team at [redacted] or toll free at [redacted]. You can also write to the Stanford IRB, Stanford University, [redacted]

EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

As a research participant you have the following rights. These rights include but are not limited to the participant's right to:

- be informed of the nature and purpose of the experiment;
- be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized;
- be given a description of any attendant discomforts and risks reasonably to be expected;
- be given an explanation of any benefits to the subject reasonably to be expected, if applicable;
- be given a disclosure of any appropriate alternatives, drugs or devices that might be advantageous to the subject, their relative risks and benefits;
- be informed of the avenues of medical treatment, if any available to the subject after the experiment if complications should arise;
- be given an opportunity to ask questions concerning the experiment or the procedures involved;
- be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation without prejudice;
- be given a copy of the signed and dated consent form; and
- be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion or undue influence on the subject's decision.

Signing your name means you agree to be in this study and that you were given a copy of this consent form.

_____ _____

Signature of Adult Participant Date & Time

_____

Print Name of Adult Participant

_____ _____

Signature of Person Obtaining Consent Date & Time

_____

Print Name of Person Obtaining Consent