Subject's Name: **Date:**

Principal Investigator: Stephen J. Savage, MD

Study Title: Vitamin D supplementation in RNA-seq profiles of single core prostate biopsy samples, including diversity and stress determinants, among Veterans. (IRB # 85140)

SUMMARY:

You are being asked to volunteer for a research study. Research studies are voluntary and include only people who choose to take part. This is a research study to find out if taking vitamin D_3 for a year has any effect on the molecular make-up of prostate tissue over time. Participants will agree to have an extra prostate tissue core collected during a routine prostate biopsy for the molecular analysis.

Your pathology report will be reviewed by your Urology physician. If it indicates prostate cancer and you decide, after discussion with your Urologist, that you will follow the plan of "active surveillance" (no immediate active treatment), you will be asked to participate in the second phase of the study. This includes three study visits that will be scheduled six months apart. Activities at each visit are listed in the Procedure section below and include blood samples for measuring body stress and vitamin D level, answering a survey and taking vitamin D_3 as a supplement every day for a year.

Routinely, after a year, you will have a repeat prostate biopsy in order to determine if the prostate cancer has progressed. At that time, as part of the research study, you will have blood samples collected for measuring body stress and vitamin D level and an extra prostate tissue core collected during your prostate biopsy.

You may or may not benefit from participating in this study. There is a risk of loss of confidentiality, but the researchers will code the samples and research information to protect privacy. Taking vitamin D_3 at 4,000 IU daily poses no risk to you.

If you are interested in learning more about this study, please continue to read below:

A. PURPOSE OF THE RESEARCH

This study is being sponsored by the National Institute of Minority Health of Minority Health and Health Disparities and is being done at this VA only. The purpose of this study is to use the available technology of RNA-sequencing (RiboNucleic Acid) to determine the molecular pathways utilized by prostate tissue and how these pathways (a) differ between African Americans and Caucasians; (b) change after supplementing with vitamin D for one year; (c) are affected by body stress and (d) are affected by ancestry. You are being asked to participate because you are scheduled to have a prostate biopsy. The investigator in charge of this study is Dr. Stephen J. Savage. Approximately 250 volunteers will be asked to give a prostate tissue sample for Part 1 of this study. From those 250 volunteers, 60 will be invited to participate in Part 2.

Subject's Name: **Date:**

Principal Investigator: Stephen J. Savage, MD

Study Title: Vitamin D supplementation in RNA-seq profiles of single core prostate biopsy samples, including diversity and stress determinants, among Veterans. (IRB # 85140)

B. PROCEDURES

If you agree to be in this study, the following will happen:

PART 1

a. You will be asked to sign this consent form when you understand all the procedures and study visit timelines required to participate.
b. During your scheduled prostate biopsy, in addition to the 12 biopsy core samples that are taken as part of routine standard of care, a 13th core sample will be obtained for research purposes only.
c. Your prostate tissue may have its RNA analyzed. RNA is considered genetic material and has a major role in making proteins, which are the building blocks of your body, cells and organs.
d. Your prostate tissue sample for RNA sequencing will be labeled with your assigned code that has no personal identifiers and only study personnel can link it back to you. Researchers outside the Veterans Affairs (VA) will not be given the link between the code and your name or other identifying information.
e. The pathology results from your biopsy will be reviewed by the research team as well as your Urology physician.
f. You will have a follow-up appointment in the VA Urology Clinic to review your biopsy report with the Urology physician. You will review and discuss your treatment options, depending on your diagnosis.
g. If you choose a treatment plan of active surveillance [standard of care recommends: repeat PSA (prostate specific antigen) at six and twelve months and repeat prostate biopsy at twelve months] and you are willing to continue your participation in this study, *you will be advanced to Part 2*.

PART 2

a) Researchers will check your medical records to gather information about your general health status, which will include laboratory results related to body stress. They will also follow your records from the Urology Clinic.

b) Your blood pressure, heart rate and weight will be measured. You will also have your hips and waist circumference measured with a tape measure.

c) You will have blood collected for vitamin D level, blood sugar, cholesterol, kidney function and stress hormones (2 tablespoons or 30mL).

d) You will be given a bottle of vitamin D softgels each containing 4,000 IU. You will take one softgel every day. If you already take vitamin D daily, please let your study team know. Taking

vitamin D for prostate cancer is considered experimental and has been cleared by the FDA (Federal Drug Administration) for studies involving prostate cancer and vitamin D supplementation.

e) You will be asked to complete a "Social Determinant" survey. You may finish the surveys in the clinic or complete them at home and mail them back in. If you have not returned the survey, a member of the study staff will contact you by phone. You will then have the option of completing the survey over the phone with a member of the study team.

Part 2: 6 Month Visit

a) You will be asked to come in 6 months after you start Vitamin D. You will be given a new bottle of Vitamin D and asked to return your old bottle to the research clinic. Please return the bottle even if there are softgels remaining in the bottle.
b) You will have blood collected for vitamin D as part of the research study. You will also have a PSA (prostate specific antigen) drawn as standard of care recommends. (1 tablespoon or 15mL).

Part 2: 1 Year- Final Study Visit and Repeat Prostate Biopsy

a) Your blood pressure, heart rate and weight will be measured. You will also have your hips and waist circumference measured with a tape measure.
b) You will have blood collected for vitamin D, PSA, blood sugar, cholesterol, kidney function and stress hormones and ancestry markers (2 ½ tablespoons or 45mL).
c) You will be asked to return your bottle of Vitamin D. Please return the bottle even if there are softgels remaining or it is empty.
d) During your scheduled prostate biopsy, in an addition to the 12 biopsy core samples that are taken as part of routine standard of care, a 13th core sample will be obtained for research purposes only.
e) Your prostate tissue samples for RNA sequencing will be labeled with your assigned code and analyzed at the Genomics Core Laboratory at Queens University Belfast, in Ireland.

While participating in this research study, do not take part in any other research project without approval from the investigators. This is to protect you from possible injury from things such as extra blood drawing, extra x-rays, or potential medication interactions. Taking part in other research studies without first discussing it with the investigators of this study may invalidate the results of this study, as well as that of the other studies.

Subject's Name: **Date:**

Principal Investigator: Stephen J. Savage, MD

Study Title: Vitamin D supplementation in RNA-seq profiles of single core prostate biopsy samples, including diversity and stress determinants, among Veterans. (IRB # 85140)

C. DURATION

Participation in Part 1 of this study is one visit on the day of your prostate biopsy. Participation in Part 2 of this study is approximately 1 year with three visits. Each visit will take approximately 30 minutes to complete.

D. RISKS AND DISCOMFORTS

Participating in this study has the following risks:

1) *Genetic Risks:* Genetic research studies may present unique risks to human subjects and their relatives. These involve medical, psychosocial and economic risks, such as the possible loss of confidentiality (private information), loss of insurability and employability, paternity, and social stigmas. Knowledge of one's genetic make-up may also affect one's knowledge of the disease risk status of family members. Genetic research raises difficult questions about informing you and other subjects of any results, or of future results. Some people feel anxious about the possibility of having a defective gene that would place them or their children at risk. Some people want to know what is found out about them; others do not. The risks of knowing include anxiety and other psychological distress. The risks of not knowing what is found include not being aware if there is treatment for the problem being studied. But these risks can change depending on whether there is a treatment or cure for a particular disease and on how clear the results are. If there is a medical reason to seek specific information from you, your doctor will tell you this. A process called "genetic counseling" is often appropriate in such cases; you should ask your doctor or nurse about this if you have any questions.

South Carolina law, mandates that your genetic information obtained from any test or from this research, be kept confidential. Our state law prohibits an insurer using this information in a discriminatory manner against your or any of your family in issuing or renewing insurance coverage for you or your family. Our state law further prohibits our sharing your genetic information with anyone except in a few narrow circumstances, one of these being a research project of this type, approved by the Institutional Review Board and then we must take all steps to protect your identity. You will still be responsible for paying for health care, however. The Ralph H. Johnson will not be responsible for such costs, even if care is needed for a condition revealed during research or clinical testing.

A federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:
• Health insurance companies and group health plans may not request your genetic information that we get from this research.
• Health insurance companies and group health plans may not use your genetic information when

making decisions regarding your eligibility or premiums.
• Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

Be aware that this new federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance, nor does it protect you against genetic discrimination by all employers.

For this study, The RNA-sequencing will analyze profiles and biological pathways on the molecular level in prostate tissue. It is not identifying specific genes and an individual's predisposition to a particular diagnosis or disease process. The ancestry markers will be analyzed for racial origin/significance only. No DNA analysis for disease identifiers will be performed.

2) *Drawing blood:* drawing blood from your arm includes a momentary discomfort and/or bruising. Infection, excess bleeding, clotting or fainting is possible, although unlikely.

3) *Loss of Confidentiality:* There is a risk of loss of confidentiality of your personal information that is used in this study. However, an assigned code, using no personal identifying information, will be assigned to you and used for all data that is shared. No names or personal identifiers will be used in any scientific presentations or publications.

4) *Taking vitamin D supplementation*. To date, hundreds of volunteers have taken 4,000 IU of vitamin D during our previous research studies with no signs of toxicity. According to the Endocrine Society and Institute of Medicine standards, a vitamin D blood level between 30-50 ng/mL is sufficient. Taking 4,000 IU of vitamin D3 daily will not exceed that level in your blood. Therefore, this research study amount of 4,000 IU daily should not produce any risk.

5) *Completing the Survey:* Some of the questions the survey asks may be upsetting, or you may feel uncomfortable answering them. If you do not wish to answer a question, you can skip it and go to the next question.

6) *Collecting an extra prostate tissue core:* Collection of an extra prostate tissue (punch) core from the outer area of the prostate will not significantly create more risk than the standard 12 (punch) core collection incurred during the routine procedure. The collection from this area will not interfere with the Pathologist's analysis of your prostate tissue and the follow-up diagnosis.

Subject's Name: **Date:**

Principal Investigator: Stephen J. Savage, MD

Study Title: Vitamin D supplementation in RNA-seq profiles of single core prostate biopsy samples, including diversity and stress determinants, among Veterans. (IRB # 85140)

There is always a chance that any procedure can harm you. The procedures in this study are no different. In addition to the risks described above, you may experience a previously unknown risk or side effect. Risks of the usual care you receive are not risks of this study. Those risks are not included in this consent form. You should talk with your healthcare providers if you have any questions about the risks of usual care.

E. MEDICAL RECORDS and/or CERTIFICATE OF CONFIDENTIALITY

This research is covered by a Certificate of Confidentiality from the Federal government. This means that the researchers may not disclose information or biospecimens that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, nor can the information or biospecimens be used as evidence, unless you have consented to this disclosure. Information or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

A Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you are a VA patient you have a VA medical record. If you have never been a VA patient, a VA medical record will be created for the purposes of this study. Results of research tests or procedures will be included in your VA medical record. All information within your medical record can be viewed by individuals authorized to access the record. We will make every effort to keep confidential all research information in the medical record that identify you to the extent allowed by law; however, there is the possibility that your research information will be disclosed.

The Certificate of Confidentiality will not be used to prevent disclosure as required by federal, state, or local law. Examples of required disclosure include: child abuse and neglect, or harm to self or others

Finally, a Certificate may not be used to withhold information from the Federal government needed for auditing or evaluating Federally funded projects or information needed by the FDA.

F. BENEFITS

There may be no direct benefit to you from participating in this study. However, it is hoped that the information gained from the study will help the researcher learn more about prostate cancer

Subject's Name: **Date:**

Principal Investigator: Stephen J. Savage, MD

Study Title: Vitamin D supplementation in RNA-seq profiles of single core prostate biopsy samples, including diversity and stress determinants, among Veterans. (IRB # 85140)

G. COSTS

You will not be charged for any treatments or procedures that are part of this study. If you usually pay co-payments for VA care and medications, you will still pay these co-payments for VA care and medications that are not part of this study.

H. PAYMENT TO PARTICIPANTS

Part 1: In return for your extra time, effort and travel expenses, you will be paid $50 in cash or will receive a $50 Visa card for participation. You will receive your payment at the time of your prostate biopsy.

Part 2: If you complete the survey and return it in the provided stamped envelope, you will receive a $15 gift card by mail**.** At your final study visit, when you have your scheduled repeat prostate biopsy, you will receive $50 cash or a $50 Visa card for your extra time, effort and travel expenses.

The IRS requires a tax form be filed if your compensation exceeds $600.00/year. However, if the payment for participation will be made through Austin Financial Services Center, it may require the use of our social security number and may generate IRS Form 1099 automatically, regardless of the amount.

I. ALTERNATIVES

If you choose not to participate in this study, you will receive standard of care prostate biopsies (without the extra core sample for research purposes) and standard treatment following your prostate biopsy results.

J. DATA SHARING

No information about you that is collected as part of this research (whether or not it is identifiable) will be used or distributed for future research studies under any circumstances.

K. DISCLOSURE OF RESULTS

Part 1: Your results from your prostate biopsy will be shared with you by your Urology physician at your follow up visit.

Part 2: Your laboratory results (cholesterol and blood glucose) will automatically be entered into the VA electronic medical record and can be viewed by your Health Care Provider and reported to you. Your blood pressure, heart rate and waist/hip measurements will be shared with you when they are obtained.

Subject's Name: **Date:**

Principal Investigator: Stephen J. Savage, MD

Study Title: Vitamin D supplementation in RNA-seq profiles of single core prostate biopsy samples, including diversity and stress determinants, among Veterans. (IRB # 85140)

The RNA prostate tissue analysis and the blood ancestry analysis will be completed only if you participate in the second part of the study. These are very complicated procedures and require extremely long, coded reports. These results will not be reported to you. However, the overall findings for all the participants will be published at the completion of the study. All results will remain de-identified (containing no personal information).

L. SIGNIFICANT NEW FINDINGS

If there are significant new findings during the course of your participation in this study, you will be notified.

M. EMPLOYEE PARTICIPATION

Your participation or discontinuance will not constitute an element of your job performance or evaluation nor will it be a part of your personnel record at this Institution.

N. CLINICAL TRIALS.GOV

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

O. COLLECTION OF SPECIMENS

- Your blood samples for PSA, cholesterol, blood sugar and kidney function will be evaluated by the VA laboratory. These results will be automatically entered into your VA electronic medical record and can be reviewed with your primary health provider.
- Your blood sample for vitamin D level and several of the blood chemistries measuring stress will be labeled with your assigned code and measured by laboratories at MUSC. Because these samples are coded, you will not receive these results.
- The sample for ancestry markers will also be labeled with your assigned code and will be analyzed at a specialized lab in California. You will not receive the results.
- The extra core prostate tissue sample will be labeled with your assigned code. Because of the complexity of the RNA-sequencing, you will not receive results.
- No samples will be stored for future research and any remaining blood or tissue samples will be destroyed by the end of the study.

Subject's Name: **Date:**

Principal Investigator: Stephen J. Savage, MD

Study Title: Vitamin D supplementation in RNA-seq profiles of single core prostate biopsy samples, including diversity and stress determinants, among Veterans. (IRB # 85140)

P. FUTURE CONTACT

In the future, we may want to contact you again to see if you'd be interested in allowing another prostate tissue specimen to be collected at the time of a regularly scheduled prostate biopsy. You will be asked to sign another consent if you agree. By initialing below, you have only agreed to allow us to contact you again in the future**.** If we may contact you again, please indicate below.

YES_____ (initial) you may contact me again for future research

NO _____ (initial) please do not contact me again for future research

CONSENT

Results of this research will be used for the purposes described in this study. This information may be published, but you will not be identified. Information that is obtained concerning this research that can be identified with you will remain confidential to the extent possible within State and Federal law.

The investigators associated with this study, the sponsor, and the Food and Drug Administration (FDA) will receive copies of the research records. The investigators associated with this study, employees of the sponsor, the FDA, and the MUSC Institutional Board for Human Research will have access to identifying information. All records in South Carolina are subject to subpoena by a court of law.

The VA will provide necessary medical treatment to a research subject injured by participation in a research project. This requirement does not apply to treatment for injuries that result from non-compliance by a research subject with study procedures. If you sustain an injury as a direct result of your study participation, medical care will be provided by this VA Medical Center. Financial compensation is not available for such things a lost wages, disability or discomfort due to an injury.

Your participation in this study is voluntary. You may refuse to take part in or stop taking part in this study at any time. You should call the investigator in charge of this study if you decide to do this. Your decision not to take part in the study will not affect your current or future medical care or any benefits to which you are entitled.

The investigators and/or the sponsor may stop your participation in this study at any time if they decide it is in your best interest. They may also do this if you do not follow the investigator's instructions.

Subject's Name: **Date:**

Principal Investigator: Stephen J. Savage, MD

Study Title: Vitamin D supplementation in RNA-seq profiles of single core prostate biopsy samples, including diversity and stress determinants, among Veterans. (IRB # 85140)

VOLUNTEER STATEMENT

Dr. Savage or a member of his research team has explained the research study to me. I have been told of the risks or discomforts and possible benefits of the study. I have been given a chance to ask questions and obtain answers.

If I have more questions about my participation in this study or study related injury, or if I have comments, concerns or complaints, I may contact: Stephen J. Savage, MD (843.789.7816).

If I have questions about my rights as a study participant, or I want to make sure this is a valid VA study, I may contact the Medical University of South Carolina's Institutional Review Board (IRB). This is the board that is responsible for overseeing the safety of human participants in this study. I may call the MUSC IRB (843) 792-4148, or the Ralph H. Johnson VA Medical Center's Research Compliance Officer at (843) 789-7399, if I have questions, complaints, or concerns about the study or if I would like to obtain information or offer input.

By signing this document below, I voluntarily consent to participate in this study. I also confirm that I have read this consent, or it has been read to me. I will receive a copy of this consent after I sign it. [A copy of this signed consent will also be scanned into your medical record].

I agree to participate in this research study as has been explained in this document.		
_____ Participant's Name	_____ Participant's Signature	_____ Date
_____ Name of person obtaining consent	_____ Signature of person obtaining consent	_____ Date