PILOT STUDY TO ANALYZE INTRAMUSCULAR MECHANISMS OF ANDROGEN DEPRIVATION RELATED SARCOPENIA

[MIRB #01653]

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Abstract

Over 200,000 new cases of prostate cancer (PCA) are diagnosed in the U.S. annually. Over the last two decades there has been a trend towards diagnosing less advanced disease, but more recently with a decrease in PSA-based screening for PCA, there has been concern that the incidence of metastatic disease will again rise. For the last 60 years androgen deprivation therapy (ADT) has remained the standard treatment for advanced and metastatic PCA. At this time, however, nearly 400,000 men remain on ADT for advanced PCA. As their disease progresses, additional therapies rely on greater suppression of androgen or inhibition of androgen targets. The impacts of ADT on men are great including sarcopenia, frailty, insulin resistance, obesity, loss of quality of life, and increased cardiovascular disease. Furthermore, age related testosterone deficiency may exert similar effects on aging men without PCA.

Despite the large number of men being treated with ADT, there is a surprising paucity of research in humans to explain the mechanism of sarcopenia and its effects. How these changes are manifested histologically also remains unknown but may involve overall loss of muscle fibers, change in distibtrution of muscle fiber types, and distribution of satellite cells. Several hypotheses have been developed to explain the mechanism of ADT-related sarcopenia but the most plausible seems to be based upon an imbalance between opposing anabolic and catabolic pathways and cross-talk between these pathways. Androgens, the growth hormone/insulin-like growth factor-1 (GH/IGF1) axis, and follistatin activate anabolic pathways. While myostatin (a negative regulator of muscle mass and a member of the transforming growth factor β superfamily) and ubiquitin ligases regulate catabolic pathways.

This is a pilot study to test the hypothesis that men on ADT will experience loss of muscle mass, loss of strength, loss of bone density, increased adiposity, and increased insulin resistance and that these changes will correspond to histologic alterations in skeletal muscle and change in relative expression of anabolic and catabolic pathway markers.

This is very relevant to our Veterans since PCA remains one of the most commonly diagnosed cancers in this population with profound side effects of ADT in this population that affect function, comorbidity, and quality of life (QOL).

List of Abbreviations

6MWT: 6-minute walk test
ADT: Androgen deprivation therapy
AIDS: acquired immunodeficiency syndrome
ALT: alanine aminotransferase
AST: aspartate aminotransferase
CHF: congestive heart failure
COPD: chronic obstructive pulmonary disease
DXA: dual-energy x-ray absorptiometry
EORTC QLQ-30: European organization for the research and treatment of cancer quality of life questionnaire
EPIC: expanded prostate cancer index composite
FACT-P: functional assessment of cancer therapy-prostate
GH: growth hormone
GnRH: gonadotropin-releasing hormone
HGS: hand grip strength
IGF: insulin-like growth factor
IGFBP: insulin-like growth factor binding protein
MRS: magnetic resonance spectroscopy
OS: optical spectroscopy
PCA: Prostate cancer
PHI: protected health information
PSA: prostate specific antigen
QOL: Quality of life
SCP: stair climb power
TCMI: translational center for metabolic imaging

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2.0 Introduction

Over 200,000 new cases of prostate cancer (PCA) are diagnosed in the U.S. annually. Over the last two decades there has been a trend towards diagnosing less advanced disease, but more recently with a decrease in PSA-based screening for PCA, there has been concern that the incidence of metastatic disease will again rise. For the last 60 years androgen deprivation therapy (ADT) has remained the standard treatment for advanced and metastatic PCA. At this time, however, nearly 400,000 men remain on ADT for advanced PCA. As their disease progresses, additional therapies rely on greater suppression of androgen or inhibition of androgen targets. The impacts of ADT on men are great including sarcopenia, frailty, insulin resistance, obesity, loss of quality of life, and increased cardiovascular disease. Furthermore, age related testosterone deficiency may exert similar effects on aging men without PCA.

Despite the large number of men being treated with ADT, there is a surprising paucity of research in humans to explain the mechanism of sarcopenia and its effects. How these changes are manifested histologically also remains unknown but may involve overall loss of muscle fibers, change in distribution of muscle fiber types, and distribution of satellite cells. Several hypotheses have been developed to explain the mechanism of ADT-related sarcopenia but the most plausible seems to be based upon an imbalance between opposing anabolic and catabolic pathways and cross-talk between these pathways. Androgens, the growth hormone/insulin-like growth factor-1 (GH/IGF1) axis and follistatin activate anabolic pathways. While myostatin (a negative regulator of muscle mass development and a member of the transforming growth factor β superfamily) and ubiquitin ligases regulate catabolic pathways.

This is a pilot study to test the hypothesis that men on ADT will experience loss of muscle mass, loss of strength, loss of bone density, increased adiposity and increased insulin resistance and that these changes will correspond to histologic alterations in skeletal muscle and change in relative expression of anabolic and catabolic pathway markers.

This is very relevant to our Veterans since PCA remains one of the most commonly diagnosed cancers in this population with profound side effects of ADT in this population that affect function, comorbidity, and quality of life.

3.0 Objectives

This is a pilot study to test the hypothesis that men on ADT will experience loss of muscle mass, loss of strength, loss of bone density, increased adiposity, and increased insulin resistance and that these changes will correspond to histologic alterations in skeletal muscle and change in relative expression of anabolic and catabolic pathway markers. We will also identify functional changes, as will cytokine, chemokine, GH levels, and other markers of inflammation and anabolic function in subject plasma. Additionally, we will correlate muscle changes with non-invasive testing with magnetic resonance spectroscopy (MRS) for muscle energetics and optical spectroscopy (OS) for mitochondrial function and cell energetics. Data obtained in the study will not be used for future research and will be used only for purposes outlined in this protocol.

4.0 Resources and Personnel

- Work will be conducted 1) within the VA at Dr. Garcia's dedicated research space, at the Clinical Research Unit, and in the Urology clinic, and 2) at the Translational Center for Metabolic Imaging (TCMI) located at the University of Washington School of Medicine.
- Dr. Garcia is the PI of the study and will oversee all study procedures including recruitment, consenting, administering surveys, performing data analysis, and coordinating all regulatory activities. Dr. Dash will identify and recruit prostate cancer patients seen in the Urology clinic at the VA and will be performing the study procedures occurring there. Lab technicians at the TCMI will be conducting the MRS and OS. Only VA personnel listed here will have access to protected health information (PHI).

5.0 Study Procedures

5.1 Study Design

One group will be included in this pilot study: Patients with advanced or metastatic PCA initiating treatment with primary ADT with a gonadotropin-releasing hormone (GnRH) agonist. This group will include 60 subjects.

There will be 4 study visits: 1) Screening, 2) Baseline, 3) Three-month visit and 4) Six-month visit. Screening will be performed within 3 weeks prior to baseline. Informed consent will be obtained prior to any screening visit procedures. Informed consent will be scanned and entered into our electronic medical records per current VA guidelines. The subject's PHI that will be needed for pre-screening and recruitment for this study is as follows; full medical history, name,

date of birth, social security number, demographics, age, telephone number, and home address. The patients that will be identified via chart review are patients of the VAMC Cancer Center.

Review of inclusion/exclusion criteria and completion of informed consent will occur at the Screening visit, followed by review of medical history and a blood draw for safety laboratory measures.

The following procedures will take place at the Baseline visit: Dual-energy x-ray absorptiometry (DXA) scan to measure body composition. Muscle performance as measured by hand grip strength (HGS), stair climb power (SCP), actigraphy, and 6-minute walk test (6MWT). Indirect calorimetry to measure VO_2 peak. Fatigue and HR-QOL assessments by EORTC QLQ-30, EPIC Hormonal, and FACT-Prostate. Magnetic resonance spectroscopy (MRS), optical spectroscopy (OS), and muscle biopsy to measure muscular mitochondrial function. Blood samples will be collected to assess degree of androgen deprivation (total and free testosterone).

All study procedures performed at baseline will be repeated at the 3- and 6- month visits with the exception of the muscle biopsy that will be performed at baseline and at the 6-month visit. Disease severity and disease progression will be assessed at each visit by measuring PSA level, and assessing stage, histologic grade (Gleason score and pattern) metastatic volume, secondary therapy, and castrate sensitivity status. Other clinical parameters to be captured will include demographics, comorbidities, and medication use. These parameters will be used as covariates in the analyses performed. Adverse events will also be recorded at the 3- and 6- month visits.

Study procedures listed here may occur on multiple days per the patient's availability. Patients may be exempt from completing some study procedures due to physical inability from disease/treatment-related symptoms. Determination of these exemptions will be left to the discretion of the study personnel.

Subjects' **medical records** will be monitored for up to 5 years to assess for the development of complications (tumor progression, chemo response, hospital admission) and for survival.

Risks associated with study procedures:
-Blood Drawing: The risks of blood drawing include pain, bleeding, and/or a bruise where the needle was inserted. Serious complications such as blood clots or infection are very rare when proper precautions are taken.
-DXA Scan: While we do not know whether any dose of radiation is completely safe, this amount of radiation is well within the limits considered safe by federal

and state regulations. The total amount of radiation used will be extremely small—approximately 0.04 milli-rem per examination or 1 milli-rem (0.001 mSv) total and less than one-tenth the dose of a standard chest x-ray, and less than a day's exposure to natural radiation. X-rays in the diagnostic range for these exams are expected to have no side effects.

-VO2 peak: risks include abnormal heart beats, abnormal blood pressure responses, muscle cramps, muscle strain and/or joint injury, delayed muscle soreness (1 to 2 days afterwards), light headedness, fatigue, and in rare instances, heart attack. This test will be performed under the direct supervision of a trained physician in the hospital where rapid access to emergency personnel and equipment including a crash cart, ECG, vitals assessment is available.

-Muscle Biopsy: The risks of muscle biopsy include pain, bruising, infection, bleeding (including rare bleeding requiring further intervention), and/or hematoma where the biopsy needle was inserted.

-Loss of confidentiality: The risks are deemed minimal and all necessary precautions as required by the IRB and VA R&D committee will be taken.

-Functional Performance: There is a small risk of incurring injury during assessment of muscle performance. This risk will be minimized by properly instructing the participants, and by performing these tests under direct supervision of experienced research personnel.

-MRS & OS: Some people may feel claustrophobic when in the MRS or feel uncomfortable while remaining still and holding the same position during the session. This will disappear soon after getting up and walking around once MRS is done. There are no known risks to breathing more oxygen than normal for the short periods of time we use in these experiments for OS. Breathing rate may speed up a little while breathing more oxygen than usual. This will return to normal when the patient begins breathing standard room air. There may be discomfort when the blood pressure cuff is inflated including numbness or tingling, and the area under the cuff may ache. This is often done by doctors during surgery and there are not known side effects of these discomforts. For people who are more likely to develop blood clots, we do not know if having the pressure cuff inflated for several minutes at a time will further increase the risk of forming a blood clot. Patients will be given a handout with information about deep vein thrombosis. The exercise may induce muscular fatigue which will disappear soon after exercise is stopped. There may be some mild muscular soreness for a day or two after the exercise. This is a normal response that disappears on its own.

Fasting risks: You may feel hungry or dizzy or have some stomach discomfort from not eating on the days you have to fast before your visit. If you are a frequent coffee drinker, you may experience discomfort or headache from not having any caffeine. If you normally use nicotine products, you may feel the effects of not having nicotine in your system.

Data and blood specimen banking will be done at the VAPSHCS Cachexia Tissue Repository. This is a new bank under this PI.

5.2 Recruitment Methods

We expect subjects to be recruited from the VA Urology clinic through Dr. Dash and his team. Patients will be identified via chart review (pre-screening). A full medical history is needed to determine if the subject meets enrollment criteria and to analyze variables that might influence outcomes measured. This will include medical problems, treatments, and medications. The subject's private health information that will be needed for this study is as follows: full medical history, name, date of birth, social security number, demographics, age, telephone number, and home address. The PI's relationship to the subject will be investigational.

5.3 Informed Consent Procedures

1-Study staff identifies potential participants from Urology clinic via medical records,
2-Study staff reviews records to ascertain initial inclusion/exclusion criteria,
3-Study staff sends list of potential subjects to clinical staff,
4-Clinical staff brings up potential research study to patient at clinical visit and asks if they’re interested in learning more,
5-Study staff then speaks with patients to provide more information,
6-If subject is interested they sign a consent form,
7-Study procedures are initiated (i.e. Screening visit)

Patients will be assured of the voluntary nature of the trial and a member of the research staff will be available to answer all questions regarding the study. We will emphasize that their decision to participate in the clinical trial will not affect their treatment.

A waiver of consent is requested for identification/pre-screening. The use or disclosure of PHI involves no more than minimal risk to the individuals and the waiver will not adversely affect the privacy rights and the welfare of the individuals. The risk is minimal because: 1) only trained personnel will have access to this information, 2) information will be accessed only from our research office at the VA and kept in a locked cabinet

behind locked doors or in password-protected computers and 3) only information absolutely required for research will be obtained and recorded.

The research could not practicably be conducted without this waiver and could not practicably be conducted without access to and use of the PHI because accessing potential subjects' medical records and their last 4 digits of their SSN and name is required to approach them to explain the proposed research and consent them.

All study personnel are trained regarding human subjects' protections requirements and how to obtain and document informed consent as it is required by local and Federal VA guidelines.

5.4 Inclusion/Exclusion Criteria

Inclusion Criteria:

-Patients with histologically, cytologically or image based documented advanced or metastatic PCa initiating ADT with expected continuous treatment for a minimum of 6 months
-Willing/able to provide informed consent.

Exclusion Criteria:

-Other causes of sarcopenia such as: Liver disease (AST or ALT ≥3x normal levels)
-Renal failure (creatinine ≥2.5 mg/dL)
-Untreated thyroid disease
-Class III-IV congestive heart failure (CHF)
-AIDS
-Other cancer diagnosed within the past five years other than non-melanoma skin cancer
-severe chronic obstructive pulmonary disease (COPD) requiring home O_2
-An active, uncontrolled infection or cardiovascular disease including a recent myocardial infarction (MI), Cerebrovascular accident (CVA), arrhythmias or unstable angina (< 6 months)
-Uncontrolled diabetes (HbA1c ≥9%)
-Neuromuscular disorder contributing to sarcopenia
–Current use (within one month) of investigational agent or testosterone, high dose steroids (20 mg of prednisone/day ≥1 month), megestrol, or anticoagulants
-Previous treatment with ADT other than oral anti-androgen at initiation of ADT.

5.5 Study Evaluations

Body composition will be measured by dual energy fan-beam DXA scan. DXA scan uses low-doseradiation to determine fat mass, bone mass, and fat-free mass (whole body and segmental). Fasting is required

Functional performance will be assessed as follows: HGS, SCP, 6MWT, VO_2 peak, and actigraphy. HGS and SCP have been shown to correlate with VO_2 peak and are good tests of aerobic and functional capacity in cachectic states. HGS will be measured by a handheld dynamometer (Jamar Hydraulic Dynamometer, J.A. Preston Corp., Clifton, NJ). SCP, which allows measuring the maximal anaerobic power of the involved muscles, will be performed as follows: subjects will climb up ordinary stairs at the highest possible speed, according to their capabilities. The stairs will consist of 13 steps of 15.3 cm each, thus covering a total vertical distance of 1.99 m. An experimenter will measure the time employed to cover the test with a digital stopwatch. Anaerobic power (in Watts) will be calculated by using the following formula: "(body mass x 9.81 x vertical distance)/time" where body mass, vertical distance (i.e., 1.99 m) and time are expressed in kg, m, and s, respectively, and 9.81 m/s^2 represents the acceleration of gravity (2–3 practice trials will be allowed so that the subjects gains a good control of the performing technique). In a 6MWT, the staff will ask subjects to walk for 6 minutes in a hallway at the facility and the distance will be recorded. For the VO_2 peak test, participants will be instructed to put on a mask/mouth piece with a breathing valve to collect expired gases. Participants will be instructed to use hand signals to notify researchers about the need to stop the test. Participants will then be asked to pedal an exercise cycle at progressively harder workloads. The test will continue until the subject becomes fatigued and decides to stop, or other symptoms prohibit further exercise. Fasting is required for the VO_2 peak test. Participants may be asked to rate their perceived exertion during the test using the Borg Rating of Perceived Exertion Scale. Actigraphs will be mailed to patients ahead of their visit, information will be recorded for 7 days and collected at their visit day. The devices will be worn by the subjects on the wrist and trained research coordinators will demonstrate its use and provide subjects with instructions in person as well as in writing. Data from returned monitors will be downloaded with companion software and analyzed for activity counts, daily steps, and estimates of energy expenditure.

Questionnaires: The FACT-P, EORTC QLQ-30, and EPIC-Hormonal questionnaires/scales will be administered to assess changes in symptoms that play a role in performance such as fatigue.

Muscle biopsy: The purpose of the sample collection is the following: histologic analysis and measurement of inflammatory, anabolic, and catabolic markers, in addition to assessment of muscular mitochondrial function. Muscle biopsies will be taken from the vastus lateralis. After anesthetizing the skin and muscle fascia with 2% lidocaine, a 1-cm incision will be made, where ~300 mg of muscle tissue

will be removed by using a 5mm biopsy needle. After the procedure is completed, pressure is applied for 5-10 minutes to establish hemostasis, the incision is closed with Dermabond, and the leg is wrapped in an ace bandage. Subjects are asked to remain supine with leg elevated for 20 minutes. Subjects' blood pressure will be rechecked before allowing to stand up. Subjects will be given post care instructions including a telephone number in case of problems related to the procedure.

Blood draw (fasted morning sample): The purpose of the sample collection is the following: 60mL sample for safety labs, inflammatory/cytokine profile, anabolic markers, and anabolic and sex hormones. Blood and muscle samples will be stored in a -80^{o} freezer in the PI laboratory for no more than 5 years. The samples will be kept to allow time for analysis of the data. De-identified samples will be shared only with co-investigators listed in the IRB. The sample will be discarded after 5 years. If a subject withdraws from the study, they will not have the option to get the remaining portion of their sample back. Samples will be retained if a subject revokes authorization; however, in such as case, those samples will be stripped of identifiers and no code linking subject's identity to the sample will be kept.

MRS & OS: Patients' quadriceps muscle will be imaged using MRS while in a relaxed state and while contracting at various levels of effort. MRS and OS will also involve non-invasive imaging during an ischemic state while wearing a compression cuff and during reperfusion after the cuff is released.

5.6 Data Analysis

We will include 60 subjects (n=60). This is a pilot and exploratory study. The data generated through this trial will be used to power a future, larger clinical study and grant submissions. The sample size has been estimated based on the availability of subjects.

All variables will be summarized descriptively by treatment using non-parametric statistical methods including N, median, SEM and standard deviation. When appropriate, analyses will be done using Kruskal-Wallis for continuous variables with Bonferroni's adjustments for multiple comparisons and chi-squared for categorical variables. Appropriate transformations will be applied to the outcome changes to improve distribution toward normality. The relationship between physiologic and histologic parameters, anabolic and catabolic markers, and sarcopenia will be established.

Potential confounding factors are, body weight at diagnosis, age at diagnosis, and presence of COPD or other co-morbidity. We will adjust for potential confounding factors by including them in the analysis. To determine whether there is a significant correlation between the histology, biomarkers, physiometry, and body composition each parameter will be compared by linear regression.

Full disclosure and complete description of all endpoints will be included in public presentations of data to avoid bias. Safety, including adverse events, will be summarized descriptively by group.

5.7 Withdrawal of Subjects

It is unlikely that subjects will be withdrawn without their consent. This may happen if regulatory authorities (VA) decide to terminate the study. Participation is completely voluntary and patients may withdraw from this study at any time without any negative consequences or penalty for study withdrawal. To withdraw, patients will be instructed to advise study staff directly by calling the number in the consent form. Subjects will not have the option to get the remaining portion of their sample(s) back. Samples will not be destroyed but the sample will be kept anonymously and used for analysis.

6 Reporting

Clinical research information will be collected in case report forms that will be kept under double lock at the research site in accordance with local and Federal guidelines. Information collected will include an assessment of adverse events (AE) at each visit after enrollment in the study.

Dr. Cyrus Zabetian is a neurologist and researcher who will be the monitor for this study. Dr. Zabetian will only serve in a monitoring capacity and will not be engaged in research. Dr. Zabetian will meet the monitoring criteria as follows per DOD guidelines below:

Research monitor functions will include:

• reviewing monitoring plans and UPIRTSO reports

• overseeing data collection and analysis

In addition, the research monitor:

• may discuss the research protocol with the investigators, interview human subjects, and consult with others outside of the study about the research;

• shall have authority to stop a research protocol in progress, remove individual human subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor's report; Version: 15 April 2013 Page 4 of 7

• shall have the responsibility to promptly report their observations and findings to the IRB or other designated official and the HRPO.

The study coordinators will send Dr. Zabetian a detailed study report annually for his review. All AE/SAE's will be reported to IRB by study staff as required following IRB guidelines.

Adverse Event Management

Any untoward or unfavorable event occurring following enrollment in the study and until conclusion of the study procedures will be considered an AE. A worsening of a pre-existing condition will be considered an AE as well. A pre-existing condition which occurs with a known temporal frequency and severity (e.g., dysmenorrhea) will not be considered an AE unless the pattern or severity has changed.

Seriousness: A serious adverse event (SAE) is any AE that results in: death, permanent or significant disability, hospitalization or a prolongation of an existing hospitalization; a congenital anomaly/birth defect; or is otherwise medically alarming.
Severity: All adverse events will be rated according to the National Cancer Institute (NCI) Common Toxicity Criteria (CTCAE v4.0).

Relationship to Study Procedure: All AE will be assessed by the Investigator to establish the presumed causal relationship with the study procedure considering: a) Temporal relationship, b) Pattern consistent with known effect of the intervention, and c) Presence of other potential etiologies. AE will be assigned one of the following causal relationships: a) Unrelated (The study procedure almost certainly did not cause the event); b) Probably not related (It is more likely that the event is due to another etiology than due to the study procedure), c) Possibly related (It is equally likely that the event is due to the study procedure as it is due to another etiology), d) Probably related (It is more likely that the event is due to the study procedure than due to another etiology) and e) Definitely related (the evidence is compelling that the study procedure caused the AE).

Monitoring Adverse Events: Subjects will be monitored for the onset of AEs throughout the course of the study. Any ongoing AE will be assessed at

appropriate frequency to document the date and time of resolution of the event. All events will be followed to resolution. Certain AEs (e.g., a cerebrovascular accident) will not be expected to resolve completely; in these cases, the date and time will be recorded when the event reaches its new, stable equilibrium and any remaining residua of the event will be documented. All AEs will be followed until resolution or until stable in cases where permanent sequelae are expected.
All SAE will be reported to IRB with appropriate forms per IRB regulations (within 5 days of study staff becoming aware), all other AEs will be reported to IRB annually.

7 Privacy and Confidentiality

Data collected in this VA research study, including identifiers, will be maintained for no more than 5 years by the VA facility. All study documents containing PHI will be kept in a locked cabinet inside a locked room (in Dr. Garcia's research office 1/815) or behind VA firewall on VA password-protected computers on Dr. Garcia's secured research drive. No data containing PHI will be accessible outside the study site. The room is kept locked with the door shut. No subject data is left out of the cabinets. Confidential information will be stored on servers managed and maintained by the VA-IT program.

Lab technicians will be provided the subject study number in person when study staff accompany the patient to the TCMI lab. All paper and electronic data generated at UW for study purposes will be securely held in HSB AA025 in the TCMI.

An adequate plan exists to protect health information identifiers from improper use and disclosure to minimize the risk of loss of confidentiality as recommended by VA guidelines. No social security numbers will be requested from subjects or potential subjects via phone Adequate written assurances exist in order to ensure that the PHI will not be reused or disclosed to (shared with) any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the PHI would be permitted under the Privacy Rule to minimize the risk of loss of confidentiality as recommended by VA guidelines.

The PI, VA collaborators, and his research staff, and VA research compliance monitors will have access to identifiable information. People who ensure quality from the institutions where the research is being done, federal, and other regulatory agencies will have access to all of the research data. No one else will

have access to identifiable research data. An Accounting of Disclosure will be created and maintained for any disclosure of individually identifiable information outside the VA. The manual spreadsheet will include the date of the disclosure, nature or description of the individually identifiable information disclosed, purpose of each disclosure and the name and address of person or agency to which the disclosure was made.

8 Communication Plan

This is a single center study. All SAEs will be reported within 5 business days of study staff becoming aware of the incident the IRB.

9.0 Information Security and Privacy

Loss of confidentiality: The risks are deemed minimal and all necessary precautions as required by the IRB and VA R&D committee will be taken. Loss of confidentiality risks will be minimized by ensuring all personnel is properly trained in information security and by keeping all information secured inside locked cabinets in locked rooms inside the VA and on secure computer servers maintained by VA IT.

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No social security numbers will be requested from subjects or potential subjects via phone.

10.0 References

1. Shanely, J Vis Exp 2014