The CArdiovascular Risk Evaluation in Men with Prostate Cancer Study **(CARE-PC)**: Initial Pilot Feasibility Study to Assess Patient Awareness and Risk Mitigation

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Study Summary

Title	The CArdiovascular Risk Evaluation in Men with Prostate Cancer Study **(CARE-PC)**: Initial Pilot Feasibility Study to Assess Patient Awareness and Risk Mitigation
Short Title	CARE-PC Study for Patient CV Risk Awareness and Mitigation
IRB Number	853844
Protocol Number	UPCC 07823
Methodology	Pilot longitudinal cohort study of men with prostate cancer planned for receiving ADT, in which the feasibility, acceptability, and data quality of a CV educational and risk assessment instrument, as well as its impact on patient awareness and CV care access will be assessed.
Study Duration	18-24 months
Study Center(s)	Single-center
Objectives	Primary: To evaluate the feasibility and acceptability of a pragmatic, patient-oriented, web-based application that enables the education of patients regarding CV risks and collects CV and prostate cancer-related risk variables and CV care access data from prostate cancer patients receiving ADT. Secondary: • To evaluate the data quality of the web-based application among prostate cancer patients receiving ADT. • To preliminarily assess the impact of the web-based application on CV care access and risk mitigation among men with prostate cancer receiving ADT.
Number of Subjects	The target number of study participants is a total of 100 patients.
Main Inclusion Criteria	Eligible subjects will be drawn from a population of patients with prostate cancer who meet the following eligibility criteria: • Men with prostate cancer > 18 years of age who are currently receiving or will be receiving treatment with ≥ 6 months of ADT • Patients must be able to read and understand English.

Statistical Methodology	Data analysis will primarily be descriptive, in keeping with the pilot nature of this project. Standard methods will be used to compute means, standard deviations, and proportions of clinical variables of interest. Distributions of patient clinical and sociodemographic factors will be summarized using standard descriptive statistics. We will calculate the web-application completion rate as the proportion of registered and completed applications among the total approached population. The Chi-square test will be used to test differences for categorical variables, analysis of variance and Kruskal-Wallis test will be used for normally distributed and non-normally distributed continuous variables, respectively.
Data Monitoring Plan	The Principal Investigator and the Penn CTSRMC will be monitoring this study and ensure ongoing quality and integrity of the research study. In addition, the study will have a yearly review by the Penn IRB.

Introduction

This document is a protocol for a human research study. This study will be conducted in full accordance with all applicable University of Pennsylvania Research Policies and Procedures, and all applicable Federal and state laws and regulations.

1 Background and Study Rationale

1.1 Cardiovascular (CV) Disease is a Major Source of Morbidity and Mortality in Men with Prostate Cancer

Cardiovascular (CV) disease and cancer are the leading causes of death in the United States. (1) In particular, among men with prostate cancer, CV disease is highly prevalent, and often represents a source of morbidity and/or mortality in excess of cancer-related risk. In fact, multiple reports evaluating the cause of death in men with prostate cancer have identified noncancer-related events, specifically ischemic heart disease, as the most common cause of mortality. (2, 3) For example, in a US population-based study, among 29,048 men with local/regional prostate cancer, the prostate cancer-specific mortality rate was 17%, while the CV disease-related mortality was 23%. (4) Additionally, even among men with metastatic prostate cancer, which carries the greatest risk for prostate cancer-specific mortality, while 75% of patients died from prostate cancer, the standardized mortality ratio for CV disease was 1.48 (95% confidence interval: 1.41-1.54), thereby indicating that men with metastatic prostate cancer remain at higher risk for CV death than members of the general population.

1.2 Shared Epidemiologic and Cancer Therapy-Related Factors Contribute to Increased CV Risk in Men with Prostate Cancer

Significant recent improvements in the management of locoregional and advanced prostate cancer have fortunately enabled many men to achieve prolonged survival. However, as this prolonged disease course typically affects an elderly male population with comorbid medical conditions, competing health risks and the prospect for treatment-related morbidity are widely recognized. (5, 6)

Systemic androgen deprivation therapy (ADT), most commonly with the use of gonadotropin-releasing hormone (GnRH) agonists or antagonists, remains the fundamental therapy for men with advanced prostate cancer, as well as a critical adjunctive therapy for many men with localized disease receiving radiation therapy with curative intent. Although deep androgen suppression achieved with ADT typically provides a rapid and robust anticancer response, it is also associated with a variety of metabolic consequences, including changes in weight and body fat distribution, lipid profiles, arterial stiffness, sarcopenia, and insulin resistance. (7) Moreover, systemic ADT exposure may modify underlying patient CV risk. Indeed, several large, retrospective analyses of administrative datasets have indicated that ADT exposure is associated with a 10-38% increased risk of CV disease and a 17% increased risk of CV mortality. (8-10) The preponderance of observational evidence indicates that these risks may be greatest in men with underlying CV disease and/or CV risk factors.

Consequently, given the recent practice trends favoring the earlier use of ADT, treatment intensification with androgen receptor signaling inhibitor (ARSI) therapies (which may potentiate CV risks), and prolonged therapeutic exposures for men with prostate cancer, an improved awareness, recognition, and mitigation of CV toxicity is needed.

1.3 CV Risk Factors are Highly Prevalent, Under-Recognized, and Under-Treated in Men with Prostate Cancer

Several published studies from our group and others have demonstrated the high prevalence of CV disease and risk factors among men with prostate cancer. However, these studies have additionally demonstrated the vast under-recognition and suboptimal management of CV risk factors in these at-risk patients. The Role of Androgen Deprivation Therapy in CVD: A Longitudinal Prostate Cancer Study (RADICAL-PC) is a large, prospective cohort of Canadian men with prostate cancer, led by principal study scientist D. Leong (Co-I). Among 2492 consecutive men with prostate cancer, 69% had a CV risk factor profile consistent with a high predicted risk of future CV disease events (i.e. 20% 10-year CVD risk). This observation was driven by preventable or modifiable risk factors, including rates of diabetes, hypertension, and current or former smoking of 16%, 45% and 58%, respectively. (11)

In further unpublished analyses of this data, we observed that CV risk factors are often under-recognized or inadequately controlled in this population: 23% of participants had hypertension that was unknown to them (defined as blood pressure ≥140 mmHg systolic and/or ≥90 mmHg diastolic in the absence of known hypertension diagnosis); 73% had blood pressure above guideline-recommended levels; 10% were current smokers; 31% had a body-mass index in the obese category (≥30 kg/m^2); 8% had an HbA1c ≥ 7%, indicating inadequate blood glucose control; 13% had a low level of physical activity as defined by the International Physical Activity Questionnaire; and 36% had low density lipoprotein (LDL) cholesterol levels above guideline-recommended levels.

Similarly, in a cross-sectional analysis of over 90,000 US veterans newly diagnosed with prostate cancer co-led by V. Narayan (PI), 68% of patients received a comprehensive CV risk factor assessment (as defined by measurement of blood pressure, cholesterol level [either LDL or total cholesterol], and blood glucose level within 1 year of prostate cancer diagnosis). (12) However, 54% of those patients undergoing comprehensive CV risk factor assessment had uncontrolled CV risk factors, and 29% of patients with uncontrolled CV risk factors were not treated. Importantly, neither the presence of underlying atherosclerotic CV disease (ASCVD), nor the planned exposure to ADT, significantly affected CV risk factor assessment or management. Herein lies a critical opportunity to improve our assessment and mitigation of CV risk, particularly among patients receiving ADT.

1.4 There is a Critical Unmet Need to Improve Patient Awareness, Assessment, and Clinical Management of CV Disease and CV Risk Factors in Men with Prostate Cancer

Given the morbidity and mortality of CV disease in prostate cancer patients, the unique CV risks posed by ADT exposure, and the problematic under-recognition and under-management of CV risk factors in this population, there is a critical need to 1) improve patient awareness of CV risk, 2) implement CV risk estimation tools among men with prostate cancer receiving ADT, and 3) understand opportunities for early CV risk mitigation interventions (such as cardio-oncology referral and/or prostate cancer treatment modifications).

As described above, data from our groups and others have indicated that CV risk is highly prevalent and under-recognized among prostate cancer patients. However, patients with prostate cancer, especially recently-diagnosed patients undergoing treatment planning and initiation, are often overwhelmed with the complexities and burdens of the requisite multidisciplinary cancer care. These burdens include frequent clinical care encounters and medical procedures such as laboratory and imaging evaluations, as well as the inherent anxieties of cancer diagnosis and treatment. Thus, in the context of complex ongoing cancer care, there is a need to better understand **patient awareness of CV risks and the potential barriers** that exist to optimal CV care specifically among prostate cancer patients.

In addition, while several established CV risk estimation tools currently exist (ex: ACC/AHA pooled cohort equation risk estimator), these have largely been developed and validated in non-cancer populations, and notably do not capture or reflect prostate cancer-specific disease and treatment variables to **optimally inform CV risk within the prostate cancer clinical context.** (13) Furthermore, the impacts of such CV risk estimates specifically on CV care access and CV risk mitigation in the prostate cancer population are unknown.

Finally, an improved understanding of prostate cancer patient awareness of CV risk and their CV care preferences/access can consequently better inform **risk mitigation opportunities** among this population. Notably, findings from a large phase 3 randomized trial of the novel oral GnRH antagonist relugolix versus the GnRH agonist leuprolide demonstrated a lower incidence of major adverse CV events with relugolix, particularly in those patients with underlying CV disease history. (14) On the other hand, recent primary study results from a separate phase 3 randomized study observed no significant difference between degarelix and leuprolide exposure in major adverse cardiovascular events, a composite of all-cause death, myocardial infarction, or stroke through 12 months. (15) Importantly, although several differences in study design and statistical power are present, one key difference in study conduct in the latter study was the requirement for concurrent longitudinal monitoring by cardiologist clinicians. Thus, together these findings indicate that with improved education, awareness, and recognition, there may be both potential therapy-related modifications (i.e. appropriate use, duration, intensity, and modality of ADT, including potential GnRH antagonist therapy) and catered CV risk factor mitigation strategies (including targeted cardiology referral, primary/secondary medical prevention) that may improve overall clinical care for prostate cancer patients receiving ADT. (16)

2 Study Objectives

2.1 Primary Objective

- To evaluate the **feasibility and acceptability** of a pragmatic, patient-oriented, web-based application that enables the education of patients regarding CV risks and collects CV and prostate cancer-related risk variables and CV care access data from prostate cancer patients receiving ADT.

2.2 Secondary Objectives

- To evaluate the **data quality** of the web-based application among prostate cancer patients receiving ADT.

- To preliminarily assess the **impact** of the web-based application on CV care access and risk mitigation among men with prostate cancer receiving ADT.

3 Investigational Plan

3.1 General Design

This is a single-center, observational pilot cohort study of men with prostate cancer who are currently receiving or will be receiving treatment with ≥ 6 months of ADT. Our overarching goal is to develop mechanisms to improve CV care among such prostate cancer patients receiving ADT by increasing patient awareness of individualized CV risk estimates and mitigation opportunities. We will implement and pilot a web-based quality improvement tool to educate patients of CV risks in prostate cancer and to inform them of their individualized, estimated CV risk and guideline-based risk mitigation recommendations. We will assess the feasibility, acceptability, and data quality of this instrument, as well as preliminarily assess its impact on patient awareness and CV care access. Through this pilot study, we will better understand both the burden of CV risk across the prostate cancer treatment spectrum and the gaps in access to adequate treatment of CV risk factors.

Patients will be provided the opportunity to register for and use the CARE-PC web-based tool through an established clinical Prostate Cancer Nurse Navigator Program and/or a standard clinical care encounter for their prostate cancer. This may occur prior to or following a scheduled routine clinical encounter. The CARE-PC web-based application will be self-completed by patient and/or caregiver.

The primary outcome measure will be the web-based application completion rate. Secondary outcome measures include 1) patient acceptance and perception of the web-based application, as measured by brief embedded survey following participation in the web-based application; 2) the percent accuracy of patient-derived CV- and prostate cancer-related data elements; 3) estimates of the prevalence and management of CV risk factors/disease; 4) the rates of current cardiologist involvement in CV care; 5) the proportions of participants engaging in CV care within 6 months of CARE-PC web application participation; and 6) frequency of changes in CV risk-reducing medications within 6 months of CARE-PC web application participation

Given the high number of prostate cancer patients receiving care at the Penn Abramson Cancer Center (ACC) (N = 4321 between 2008-2020), it is anticipated that accrual will be completed over a 12-month period. Following the completion of the web-based application, patients will be followed for a period of up to 6 months (via retrospective medical record chart review) to evaluate for clinical CV care delivery in the period following completion of the tool. Clinical data and changes in CV status and care delivery will be collected through chart abstraction, as available.

3.2 Study Measures

This protocol will 1) test the feasibility and acceptability of the CARE-PC web-based application and its impact on prostate cancer patient perceptions of CV risk, 2) evaluate the quality of patient-generated CV

and cancer data obtained through the CARE-PC web-based application, and 3) preliminarily assess the impact of use of the CARE-PC web application on patient interest/access to CV care.

3.3 Study Endpoints

3.3.1 Primary Study Endpoint

The primary study endpoint will be the web-based application completion rate, measured as the proportion of participants successfully completing the web-based application out of the total number of subjects approached.

3.3.2 Secondary Study Endpoints

Secondary study endpoints will include:

- Patient perception of web-based application, as measured by brief embedded survey, following participation in the CARE-PC web-based application
- Percent accuracy of patient-derived CV- and prostate cancer-related data elements, as assessed through parallel medical chart review by cardiology and oncology clinicians
- Prevalence of CV risk factors/disease at the time of CARE-PC web-based application participation
- Proportion of participants with current cardiologist involvement in CV care at the time of web-based application participation
- Proportion of participants engaging in CV care within 6 months of CARE-PC web application participation
- Proportion of participants having changes in CV risk-reducing medications within 6 months of CARE-PC application participation.

4 Study Population and Duration of Participation

4.1 Duration of Study Participation

The duration of study participation will be 1 day (including subject registration, web-based application participation, survey completion). In addition, there will be a 6-month participant follow-up (via medical chart review), which will not require any active subject participation.

4.2 Total Number of Subjects and Sites

This is a single-site observational pilot study performed at the University of Pennsylvania Health System / Abramson Cancer Center. A total of 100 patients will undergo study procedures (including web-based application participation and survey completion). It is expected that approximately 150 patients will be approached in order to produce 100 evaluable subjects. (33% non-participation rate)

4.3 Inclusion Criteria

Eligible subjects will be drawn from a population of patients with prostate cancer who meet the following eligibility criteria:

- Men with prostate cancer > 18 years of age who are currently receiving or will be receiving treatment with ≥ 6 months of ADT
- Patients must be able to read and understand English.

4.4 Subject Recruitment

Patients receiving care within Genitourinary Medical Oncology, Radiation Oncology, and Urologic Oncology clinical practices at the Abramson Cancer Center, who meet the study eligibility criteria will be approached for potential study participation.

Healthcare providers caring for prostate cancer patients will identify potential participants (i.e. patients who are currently receiving or are planned to receive >6 months ADT) during routine healthcare encounters. An established Prostate Cancer Nurse Navigator Program within the GU Cancer Service Line may also assist with identifying potential participants through the Cancer Service Line new patient intake process. The prostate cancer healthcare provider may notify the prostate cancer nurse navigator(s) of potential participants and/or directly approach potential patients for participation.

The subject will receive all routine oncologic care as per their primary oncologic provider.

4.5 Vulnerable Populations:

Children, pregnant women, fetuses, neonates, or prisoners are not included in this research study.

5 Study Procedures

5.1 Screening and Consent

Potential subjects will be identified by the Prostate Cancer Nurse Navigator and/or healthcare providers as described in **Section 4.4**.

Following identification of a potential participant, the Prostate Cancer Cancer Nurse navigator or other designated study staff will discuss the study rationale and procedures during a routine healthcare encounter or contact the patient (via MyPennMedicine message or telephone call) following a routine healthcare encounter to discuss the study rationale and procedures. The nurse navigator or other designated study staff will additionally provide the potential participant (or send via MyPennMedicine message or email) the Study Information Sheet outlining the study rationale, procedures, benefits, and risks (**Attachment A**). If the patient verbally agrees to participate (or responds affirmatively via MyPennMedicine or email communication), then the nurse navigator or designated staff will document the participant's agreement to participate in the EMR and then send the website link for the CARE-PC application tool directly to the participant (via MyPennMedicine message or email). If the patient would like additional time to review the information on his own, the study staff will allow the patient additional time to review the document, and the CARE-PC application tool will only be sent once the participant has verbally agreed to participate (or responds affirmatively via MyPennMedicine or email communication).

The prostate cancer nurse navigator or designated staff will complete documentation of eligibility, patient agreement to participate, and date that the CARE-PC application was sent to patient in an EMR telephone encounter, and route this note to the study PI for review/co-signature.

Given the limited risk involved in this quality improvement and education initiative, participants will be enrolled with a waiver of documentation of consent. The patient's willingness to participate (through verbal, MyPennMedicine, or email affirmation) will be documented within the EMR telephone encounter, as described above, prior to the CARE-PC weblink being sent to the participant.

Once the patient has agreed to participate, and the CARE-PC weblink has been sent, the prostate cancer nurse navigator or designated staff will notify the study research coordinator of the subject's participation. The research coordinator will enter the subject into PennCTMS to record study enrollment, as well as to maintain an "honest broker" protected link between the patient MRN and study specific patient identifier (participant -01, -02, -03, etc).

If the participant has not completed the CARE-PC web-based application tool within 1 week of it being sent, the nurse navigator or designated staff may contact the patient (via telephone, MyPennMedicine message, or email) with a single reminder notice.

5.2 CARE-PC Web-Based Application Registration and Completion

Upon receiving the CARE-PC application tool link, participants will first register for an account in the CARE-PC web-based application using their email address. **No PHI, including name, MRN, date of birth, or address will be requested via the CARE-PC application.**

Following registration, participants will be prompted to enter information on their general demographics, CV health, and key prostate cancer characteristics via the study web application.

Simplified, key demographic, CV, and prostate cancer variables will be collected through the web-based tool in a patient-oriented format (**see Appendix 1 for the specific requested Data Elements in the CARE-PC web-based application**).

- Demographic and Cardiovascular Care Access data elements will include: age, gender (note: all participating prostate cancer patients will be male; however, the CARE-PC application is developed for future broader patient populations / applications), ethnicity, marital status, highest educational level, occupation, living situation, current cardiology provider involvement (yes/no), most recent cardiology encounter (within 1 month prior, 6 months prior, 1 year prior, > 1 year prior), most recent primary care provider encounter (within 1 month prior, 6 months prior, 1 year prior, > 1 year prior)

- Key CV variables will be obtained using an established patient-oriented web-based CV risk estimators, the Mayo Clinic Heart Disease Risk Calculator, which is based on Framingham 10-Year CV disease risk estimation and includes non-laboratory based estimates. (website: https://www.mayoclinichealthsystem.org/locations/cannon-falls/services-and-treatments/cardiology/heart-disease-risk-calculator).

  CV data elements will include: height, weight, race (African American, Caucasian, Hispanic, Other), prior CV disease (heart attack, stroke, aortic aneurysm, cardiac stent, peripheral artery disease, heart failure, arrhythmia), family history of CV disease, tobacco history (Have you smoked at least 100 cigarettes? Have you smoked regularly in the past 12 months?), diabetes, hyperlipidemia, obesity, most recent blood pressure (systolic blood pressure, diastolic blood pressure), laboratory lipid values (if known), cardiac medication use (anti-hypertensives, statins),

usual weekly physical activity, typical daily fruit or vegetable serving intake, typical daily saturated fat intake.

- Key Prostate Cancer Characteristics will include: Current Cancer Status (localized vs metastatic), Prior Therapies (Surgery, Radiation, ADT modalities, Chemotherapy, Other), Duration of Current/Ongoing ADT Exposures (ADT and ARSI Therapies) (6 months; 6-24 months; Indefinite/Continuous), Type(s) of Current/Ongoing ADT Exposures (check all that apply from menu)

5.3 Patient CV Risk Estimation

Patient CV Risk Estimation: The CARE-PC web application will provide *immediate* feedback to participants through their email account on their 10-year risk of adverse CV events, as estimated via the Mayo Clinic Heart Disease Risk Calculator. If lipid values are provided by the patient, then the laboratory-based CV risk estimate will be provided. If lipid values are not known or provided by the patient, then the non-laboratory-based CV risk estimate will be provided.

In addition, tailored, guideline-supported recommendations on strategies to help reduce the patient's risk of future CV disease will be included in direct-to-patient immediate feedback.

This feedback will serve two purposes: 1) it will act as incentive for patients to participate in this study (**education**) and 2) the patient education provided may enable immediate action to reduce participants' CV risk (**quality improvement**).

All participants will be encouraged to speak with their treating healthcare team to discuss the results of the risk assessment and any CV evaluations or medical consultations, as may be needed.

5.4 Assessment of CARE-PC Clinical Data Quality

The patient-derived data quality, as entered into the CARE-PC web-based application, will be assessed through parallel medical chart review by cardiology and oncology clinicians, which will represent the true standard.

A single cardiology clinician with expertise in CV risk assessment and a single medical oncology clinician with expertise in prostate cancer will be utilized. Among participants successfully completing the web-application, the patient-entered data accuracy will be compared to the medical chart-based true standard, by individual variable as well as by CV and prostate cancer-related categories.

The process for data quality review will be as follows:

The CARE-PC application will output the patient-entered data (demographics, CV health, and prostate cancer health) as described in **Section 5.2**. This patient-entered data will be directly downloaded to a .csv spreadsheet format. Notably, this output will include the study-specific patient identifier, but no PHI. The cardiology and oncology clinicians will use the patient MRN / participant ID link (held in PennCTMS by research coordinator) to perform manual chart review to assess the accuracy of patient-derived CARE-PC data downloaded to this .csv spreadsheet. (Example: If patient reports planned ADT duration of "6

months", however, medical chart review notes "indefinite/continuous", then this would be deemed "Inaccurate CARE-PC Patient-Derived Data").

This assessment of accuracy will be conducted in a Master Datasheet, which will include the de-identified .csv patient data (as downloaded directly from the CARE-PC application) and the cardiology/oncology clinician "true standard" obtained via medical chart review. The discrete elements held in this Master Datasheet for study analyses are outlined in **Appendix 2**. Notably, no PHI will be included in this Master Datasheet.

5.5 6-Month Follow-up via Medical Chart Review

Following the completion of the CARE-PC web-based application, participants will have completed the study participation. However, study investigators will perform medical chart review to evaluate for clinical CV care delivery (including cardiologist encounters, medication changes, and CV events) during the 6 months since CARE-PC application completion, as available.

5.6 Subject Withdrawal

Subjects may withdraw from the study at any time without impact to their care. It will be documented whether or not each subject completes the study CARE-PC web-based application.

6 Statistical Plan

6.1 Statistical Methods

Given the pilot nature of this project, data analysis will primarily be descriptive in nature. Baseline subject characteristics will be summarized by standard descriptive statistics (including mean and standard deviation for continuous variables, and standard proportion for categorical variables). For the primary study feasibility endpoint, the total proportion of approached patients successfully completing the CARE-PC web-based application will be reported.

Standard descriptive statistics will be used to describe the secondary endpoints of interest. Distributions of patient clinical and sociodemographic factors will be summarized using standard descriptive statistics. How application completion differs according to age, race (Black, White, Other), ethnicity, prostate cancer stage (localized versus metastatic), treatment site (medical oncology, urology, radiation oncology), marital status, and educational status will be assessed. The Chi-square test will be used to test differences for categorical variables, analysis of variance and Kruskal-Wallis test will be used for normally distributed and non-normally distributed continuous variables, respectively.

Among patients completing the web-application, the patient-entered data accuracy will be compared to the medical chart-based true standard, by individual variable as well as by CV and prostate cancer-related categories. The discordance between patient-driven 10-year CV risk estimation and actual clinician-driven 10-year CV risk estimation will be reported. How the rates of data accuracy may differ according to age, race (Black, White, Other), ethnicity, current cardiology provider involvement/access, prostate cancer stage (localized versus metastatic), treatment site (medical oncology, urology, radiation oncology), marital status, and educational status will be assessed.

The prevalence and management of CV risk factors/disease and the rates of current cardiologist involvement in CV care will be evaluated. The frequencies of CV risk factors (hypertension, diabetes mellitus, dyslipidemia, tobacco use, elevated BMI, sedentary lifestyle) and CV disease (CAD, heart failure, cardiomyopathy, CVA, arrythmia), will be tabulated overall and by prostate cancer status and treatment exposures. Similarly, the rates of cardiology clinician access and involvement will be tabulated by prostate cancer status, treatment exposure, treatment site (medical oncology, urology, radiation oncology), age, race, marital status, and educational status.

Rates of cardiology and/or preventative medicine clinician access and involvement, including new encounters and established provider encounters, within 6 months of web-based application registration/completion will be tabulated. These measures will be explored by prostate cancer stage (localized vs metastatic), presence of existing CV clinical provider, and by ADT treatment (ADT alone, ARSI therapy).

7 Study Administration, Data Handling and Record Keeping

7.1 Confidentiality

This research is covered by a Certificate of Confidentiality from the National Institutes of Health.
In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization.

The following PHI will be collected as data for this study:

- Name
- Subject date of birth
- Subject medical record number

7.2 Data Collection and Management

All study participants will be assigned a unique study ID that is not derived from any subject information. A master list of PHI (name, medical record number) and subject ID numbers will be kept separate from any study data forms, whether they be paper or electronic. This information will be kept in PennCTMS. Only authorized study personnel will have access to these files. This information will only be used by investigators to perform the specified medical chart review for data accuracy assessments and 6 month chart review follow-up, as described above.

De-identified study data will be recorded separately in a .csv Master Datasheet using only the assigned study-specific subject identifier. This Master Datasheet research database (**Appendix 2**) will be accessible only by the PI, Co-investigators, and designated research staff as described to the IRB. Any material shared with collaborators will be supplied with subject study ID numbers only, and without patient identifying information.

Additionally, the CARE-PC data entered by the patient (**Appendix 1**) is entered through a simple website survey platform via a standard internet browser and will be stored in a server that is physically located in a secure, monitored, climate-controlled room at the Population Health Research Institute, and are backed up

to the cloud using encrypted, industry-standard standards. This storage will enable the participant to log-in to the portal at a future time (using their email address) to review and print their CARE-PC cardiovascular risk profile and print/share with their treating healthcare providers.

7.3 Records Retention

Records for all subjects, including CRFs, all source documents, as well as IRB records and other regulatory documentation, will be retained by the investigator in a secure storage facility in compliance with HIPAA and the OHRP for a period of 5 years.

At the end of 5 years, identifiable patient records will be destroyed and any associating data be purged from the current database per the Cancer Center's designated destruction policy and procedures. De-identified data will be securely maintained indefinitely for research purposes.

8 Study Monitoring, Auditing, and Inspecting

8.1 Study Monitoring Plan

The Principal Investigator and the Penn CTSRMC will be monitoring this study and ensure ongoing quality and integrity of the research study. In addition, the study will have a yearly review by the Penn IRB.

8.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities.

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

9 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice, applicable government regulations, and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the conduct of the project. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator. All subjects for this study will be provided a study information sheet describing this study, collection and use of data, and providing sufficient information for subjects to make an informed decision about their participation in this study. See *Attachment A, Study Information Sheet*. The Prostate Cancer Cancer Nurse Navigator or other designated study staff will then contact the patient and review the study information sheet with the potential subject and answer any questions (as described in Section 5.1). If the potential subject decides to move forward with study participation, they will register for an account in the CARE-PC web-based application. The study information sheet will be submitted with the protocol for review and approval by the IRB for the study.

In trying to maintain ethical considerations in human research, only individuals who are able to understand and make the decision to participate will be recruited for this study (i.e. no recruitment of patients with impaired decisional capacities). In addition, no vulnerable populations, such as children (below 18 years of age), pregnant women, fetuses, neonates, or prisoners will be recruited for this study.

All project staff will have CITI and HIPAA training before the commencement of this study. The University of Pennsylvania IRB will review all staff required human research protection trainings to ensure the study is compliant with all government and University regulations.

9.1 Risks

The risk of participation in this study primarily pertains to the administration of a web-based application to educate and estimate individualized CV risk for prostate cancer patients receiving ADT. However, as this information is intended for educational purposes, there is minimal associated risk. In addition, participants will be encouraged via the web-based application to discuss the content and risk estimation results of the CARE-PC web application with their prostate cancer and/or CV healthcare providers. These risks will be included and clearly outlined in the Study Information Sheet.

9.2 Benefits

The potential individual benefit of study participation is that participants will gain evidence-based education regarding CV risk within the context of prostate cancer and ADT exposure. Furthermore, an individualized CV risk estimation, as well as potential CV risk mitigation strategies will be presented. Participants can then discuss these risk estimates and mitigation strategies with their prostate cancer and/or CV healthcare providers.

In addition, by participating in this study, participants may contribute to an improved understanding of both the burden of CV risk across the prostate cancer treatment spectrum and the gaps in access to adequate treatment of CV risk factors.

9.3 Risk Benefit Assessment

Given the minimal risk associated with the web-based application content and the potential benefits provided by education and individualized CV risk estimation, the risks of participating in the study are outweighed by the potential benefits of participating in the study.

9.4 Informed Consent Process / HIPAA Authorization

All subjects for this study will be provided a study information sheet providing sufficient information about this research and the collection and use of their data. See **Attachment A** for a copy of the Study Information Sheet. This form will be submitted with the protocol for review and approval by the IRB for the study. Potential subjects will have the opportunity to review the information sheet in detail, have the ability to take the sheet home for further review, and to ask any questions of the Principal Investigator or study staff. A written documentation of consent will not be required. However, patient agreement to participate (as outlined in **Section 5.1**) will be documented by study staff in the EMR.

10 Study Finances

10.1 Funding Source

This study will be funded through an Institutional research grant from the National Comprehensive Cancer Network.

10.2 Conflict of Interest

All University of Pennsylvania Investigators will follow the University of Pennsylvania Policy on Conflicts of Interest Related to Research.

10.3 Subject Stipends or Payments

There will be no financial compensation or equivalent provided to subjects who participate in this study.

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12 Attachments

Attachment A.

Research Study Information Sheet

See Research Study Information Sheet

Appendix 1.

Specific List of Variables Obtained via CARE-PC Web Based Application (Patient-Entered Directly into CARE-PC tool). (Note: No dates or other PHI are obtained)

Demographic and Cardiovascular Care Access:

- Age (years)
- Gender
- Ethnicity
- marital status
- highest educational level
- occupation
- living situation
- current cardiology provider involvement (yes/no)
  - Logic: most recent cardiology encounter (within 1 month prior, 6 months prior, 1 year prior, > 1 year prior)
- most recent primary care provider encounter (within 1 month prior, 6 months prior, 1 year prior, > 1 year prior)

Cardiovascular Health Variables:

- Height
- Weight
- race (African American, Caucasian, Hispanic, Other)
- prior CV disease (heart attack, stroke, aortic aneurysm, cardiac stent, peripheral artery disease, heart failure, arrhythmia)
- family history of CV disease in first degree relative
- tobacco history (Have you smoked at least 100 cigarettes? Have you smoked regularly in the past 12 months?)
- diabetes
- blood pressure (SBP, DBP)

- hyperlipidemia
- obesity
- cardiac medication use (anti-hypertensives, statins)
- usual weekly physical activity
- typical daily fruit or vegetable serving intake
- typical daily saturated fat intake

Prostate Cancer Variables:

- Current Cancer Status (localized vs metastatic)
- Prior Therapies (check all that apply) (Surgery, Radiation, ADT modalities, Chemotherapy, Other)
- Type(s) of Current/Ongoing ADT Exposures (check all that apply) [Lupron or Eligard (leuprolide), Firmagon (degarelix), Orgovyx (relugolix), Zytiga (abiraterone), Xtandi (enzalutamide), Erleada (apalutamide), Nubeqa (darolutamide)]
- Planned Duration of Current/Ongoing ADT Exposures (6 months; 6-24 months; Indefinite/Continuous)

Appendix 2.

Specific List of Variables Included in Master Datasheet for Study Analyses (Includes data entered by patient via CARE-PC Web Based Application and Medical Chart Review performed by Penn Cardiology/Oncology Clinician Investigators.
(Note: No dates or other PHI are included in the Master Datasheet)

Demographic and Cardiovascular Care Access:

- Age (years)
- Gender
- Ethnicity
- marital status
- highest educational level
- occupation
- living situation
- current cardiology provider involvement (yes/no)
  - Logic: most recent cardiology encounter (within 1 month prior, 6 months prior, 1 year prior, > 1 year prior)
  - Accurate per medical chart review (yes/no)
- most recent primary care provider encounter (within 1 month prior, 6 months prior, 1 year prior, > 1 year prior)
  - Accurate per medical chart review (yes/no)

Cardiovascular Health Variables:

- Height
  - Accurate per medical chart review (yes/no)
- Weight
  - Accurate per medical chart review (yes/no)
- race (African American, Caucasian, Hispanic, Other)
- prior CV disease (heart attack, stroke, aortic aneurysm, cardiac stent, peripheral artery disease, heart failure, arrhythmia)

  - Accurate per medical chart review (yes/no)
  - True Standard per medical chart review
- family history of CV disease in first degree relative
- tobacco history (Have you smoked at least 100 cigarettes? Have you smoked regularly in the past 12 months?)
  - Accurate per medical chart review (yes/no)
  - True Standard per medical chart review
- Diabetes
  - Accurate per medical chart review (yes/no)
  - True Standard per medical chart review
- blood pressure (SBP, DBP)
  - Accurate per medical chart review (yes/no)
  - True Standard per medical chart review
- Hyperlipidemia
  - Accurate per medical chart review (yes/no)
  - True Standard per medical chart review
- Obesity
  - Accurate per medical chart review (yes/no)
  - True Standard per medical chart review
- cardiac medication use (anti-hypertensives, statins)
  - Accurate per medical chart review (yes/no)
  - True Standard per medical chart review
- usual weekly physical activity
- typical daily fruit or vegetable serving intake
- typical daily saturated fat intake

Prostate Cancer Variables:

- Current Cancer Status (localized vs metastatic)
  - Accurate per medical chart review (yes/no)
  - True Standard per medical chart review
- Prior Therapies (check all that apply) (Surgery, Radiation, ADT modalities, Chemotherapy, Other)
  - Accurate per medical chart review (yes/no)
  - True Standard per medical chart review
- Type(s) of Current/Ongoing ADT Exposures (check all that apply) [Lupron or Eligard (leuprolide), Firmagon (degarelix), Orgovyx (relugolix), Zytiga (abiraterone), Xtandi (enzalutamide), Erleada (apalutamide), Nubeqa (darolutamide)]
  - Accurate per medical chart review (yes/no)
  - True Standard per medical chart review
- Planned Duration of Current/Ongoing ADT Exposures (6 months; 6-24 months; Indefinite/Continuous)
  - Accurate per medical chart review (yes/no)
  - True Standard per medical chart review