Title: Optimizing Veteran-Centered Prostate Cancer Survivorship Care (Phase B)

Funding Source: VA Health Services Research and Development

Principal Investigator/Study Chair: Sarah Hawley

June 14, 2017

Abstract

Provide a summary of the study (less than 500 words).

Background: Although there are over 200,000 prostate cancer survivors in the VA, there has been little research to understand and improve survivorship care for this large population of Veterans. A substantial proportion of prostate cancer survivors in the general population have significant side effects from treatment (surgery or radiation therapy) that often persist for years, including incontinence, erectile dysfunction, and metabolic syndrome, all of which can contribute to decreased quality of life. Our pilot data suggests that VA prostate cancer survivors experience similar or worse symptom burden to that of the general population of survivors. This is particularly unfortunate since many of these symptoms can be effectively self-managed. Furthermore, there is no program in the VA for assessing ongoing symptom burden in survivors and directing them to receive appropriate primary or specialty care if needed.

Objectives: To address the need to improve patient-centered survivorship care management for Veterans with prostate cancer, we propose a 4 year study with two aims: 1) to conduct a randomized controlled trial to compare a personally tailored automated telephone symptom management intervention for improving symptoms and symptom self-management to usual care. We expect that those in the intervention group will have more confidence in symptom self-management and better symptom self-management and prostate cancer quality of life following the intervention, and that these outcomes will translate to more efficient use of services for these Veterans, and 2) to compare utilization of services among those in the intervention group to those in the control group.

Methods: We will conduct a RCT of prostate cancer survivors at 4 VHA sites (Ann Arbor, Cleveland, Pittsburgh and St. Louis) who are 1-10 years post-treatment. Those with clinically meaningful symptom burden identified using an established measure of prostate cancer symptom burden will be invited to the study, verbally consented and randomized to the automated telephone system or enhanced usual care (information about self-management). We will evaluate the impact of the intervention on confidence in symptom self-management as well as actual symptom burden and prostate cancer quality of life 5- and 12-months following enrollment. We will evaluate utilization of services 9-12 months post-enrollment using medical record/CPRS data sources. Finally, we will conduct a small process evaluation that will help us to better understand which elements of the intervention were effective, and will work with our primary care partners to make a recommendation for a broader deployment of an automated symptom self-management program in the VHA.

Our study will provide much needed information about how to optimize the quality of care and quality of life of Veterans who are survivors of prostate cancer. The randomized trial will evaluate innovative information for assessing and improving symptom burden and self-management of prostate-related symptom burden in these survivors. We will further understand how symptom burden is associated with use of appropriate services in the VHA. Finally, we will work with our primary care partners to inform how to improve survivorship care for this large and growing population of Veterans.

List of Abbreviations

Provide a list of all abbreviations used in the protocol and their associated meanings.

VA – Veterans Affairs

VHA – Veterans Health Administration

AE- Adverse Events

AAVA-Ann Arbor VA

CHCR – University of Michigan Center for Health Communications Research

CDW – Corporate Data Warehouse

CPRS – Computerized Patient Record System

EPIC – Expanded Prostate Cancer Index Composite

IVR- Interactive Voice Response

MTS- Michigan Tailoring System

PACT- Patient Aligned Care Team

PC – Prostate Cancer

PCP – Primary Care Physician

PEPPI -- Perceived Efficacy in Patient-Physician Interactions

PHI- Protected Health Information

QOL- Quality of Life

RCT – Randomized Controlled Trial

SAE – Serious Adverse Event

SAS- Statistical Analysis Software

SD- Standard Deviation

SEER- Surveillance, Epidemiology and End Results registries (National Cancer Institute)

UAPs – Unanticipated Problems

VA – Veterans Affairs

VHA – Veterans Health Administration

Contents

Protocol Title:

Optimizing Veteran-Centered Prostate Cancer Survivorship Care (Phase B)

1.0 Study Personnel

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2.0 Introduction

- **Provide scientific background and rationale for study.**

Prostate cancer is the most commonly diagnosed cancer in Veterans. Over 12,000 Veterans will be diagnosed with prostate cancer in 2012 to join more than 200,000 current prostate cancer (PC) survivors, making these patients one of the largest populations in the Veterans Administration Healthcare System (VA). Data from numerous studies in the general population and our own pilot work clearly show that many Veterans with PC suffer with high symptom burden for years following their treatment, and that these symptoms contribute to poor disease specific, and overall, QOL. Our study is based on a conceptual framework for describing how self-management can work to improve outcomes for cancer survivors, including both proximal outcomes (reducing symptom burden and improving disease specific QOL) as well as longer term outcomes (subjective health and cancer outlook). Veterans in our pilot study expressed strong interest in receiving assistance with symptom management, and many of them successfully used a prototype automated telephone system in an effort to do so. Improving these outcomes is likely to translate into better Veteran-centered care for survivors of prostate cancer, one of the largest patient groups within the VA.

- **Include summary of gaps in current knowledge, relevant data, and how the study will add to existing knowledge.**

Although there are over 200,000 prostate cancer survivors in the VA, there has been little research to understand and improve survivorship care for this large population of Veterans. A substantial proportion of prostate cancer survivors in the general population have significant side effects from treatment (surgery or radiation therapy) that often persist for years, including incontinence, erectile dysfunction, and metabolic syndrome, all of which can contribute to decreased quality of life. Our pilot data suggests that VA prostate cancer survivors experience similar or worse symptom burden to that of the general population of survivors. This is particularly unfortunate since many of these symptoms can be effectively self-managed. Furthermore, there is no program in the VA for assessing ongoing symptom burden in survivors and directing them to receive appropriate primary or specialty care if needed.

To address the need to improve patient-centered survivorship care management for Veterans with prostate cancer, we propose a 4 year study with two aims: 1) to conduct a randomized controlled trial to compare a personally tailored automated telephone symptom management intervention for improving symptoms and symptom self-management to usual care. We expect that those in the intervention group will have more confidence in symptom self-management and better symptom self-management and prostate cancer quality of life following the intervention, and that these outcomes will translate to more efficient use of services for these Veterans, and 2) to compare utilization of services among those in the intervention group to those in the control group.

Our study will provide much needed information about how to optimize the quality of care and quality of life of Veterans who are survivors of prostate cancer. The randomized trial will evaluate innovative information for assessing and improving symptom burden and self-management of prostate-related symptom burden in these survivors. We will further understand how symptom burden is associated with use of appropriate services in the VHA. Finally, we will work with our primary care partners to inform how to improve survivorship care for this large and growing population of Veterans.

- **Include rationale for including or excluding certain populations – in particular vulnerable populations.**

  Veteran participants: Women are excluded as this is a condition found only in men.

3.0 Objectives

- **Describe the study's purpose, specific aims, or objectives.**

  The specific aims are:

  1) To conduct a randomized controlled trial among PC survivors with high symptom burden comparing the impact of this personalized intervention for improving symptoms and symptom self-management to nonpersonalized information. We hypothesize that relative to controls, 5- and 12- months post-enrollment, Veterans in the intervention group will: 1) have higher confidence about symptom self-management; and 2) report lower symptom burden and better disease-specific QOL. We further hypothesize that at the 12-month assessment point, the intervention group will have higher scores on two key psychosocial indicators (subjective health and perceived cancer control) than the control group.

  2) To determine the intervention's impact on the use of primary and specialty VA services. We hypothesize that relative to controls, 12 months after enrollment, Veterans in the intervention group will have a higher rate of symptom-specific service use that is consistent with Michigan Cancer Consortium recommendations for prostate cancer survivorship care, which are expert and evidence-based. This project could have a significant positive impact on the lives of the large and growing population of Veterans who are PC survivors experiencing post-treatment symptoms. Data from our preliminary work suggest that many of these survivors continue to suffer with high symptom burden years after treatment, report wanting to participate in self-management interventions, and that an automated telephone system is feasible and potentially effective. Our team has extensive expertise in the development and deployment of highly personalized, automated interventions for improving self-management in the VA, as well as the clinical and health services research expertise to successfully implement and complete the study. We have the support of the Office of Specialty Care/Patient Care Services as well as the VA Ann Arbor PACT (Patient Aligned Care Team) Laboratory. To ensure that the trial has the greatest possible impact on VA care, we will conduct a process evaluation to determine how the intervention can best optimize the quality of life and survivorship care for Veterans with prostate cancer and inform program implementation with our primary care partners.

- **State the hypotheses to be tested.**

  We hypothesize that relative to controls, 5- and 12- months post-enrollment, Veterans in the intervention group will: 1) have higher confidence about symptom self-management; and 2) report lower symptom burden and better disease-specific QOL. We further hypothesize that at the 12-month assessment point, the intervention group will have higher scores on two key psychosocial indicators (subjective health and perceived cancer control) than the control group.

4.0 Resources and Personnel

- **Include where and by whom the research will be conducted.**

  This study will be conducted by local coordinators in three sites: the VA Ann Arbor Healthcare System (VAAAHS), the VA Pittsburgh Healthcare System (VAPHS) and the St. Louis VA Medical Center (SLVAMS). The coordinating site will be the VAAAHS, where the PI and most of the research team are located. Each site has experience in the conduct of research, and sufficient numbers of PC survivors from which to identify participants for both phases of our study. VAPHS and SLVAMS sites each offer significant numbers of potentially eligible survivors who are racial/ethnic minority Veterans, especially African Americans who have a higher rate of PC. The coordinators from these three sites will also recruit patients from an additional site, the Louis Stokes Cleveland VA Medical Center (LSCVAMC) (this site will not have an assigned LSI or local coordinator).

- **Provide a brief description of each individual's role in the study. Be sure to indicate who will have access to protected health information and who will be involved in recruiting subjects; obtaining informed consent; administering survey/interview procedures; and performing data analysis.**

AAVA Study Staff:

Dr. Hawley will be responsible for the implementation of the scientific agenda, the leadership plan and the specific aims, and ensure that systems are in place to guarantee institutional compliance. She will oversee all aims of the study working in conjunction with the multidisciplinary team. Dr. Hawley will be responsible for ensuring all IRB approvals are obtained. She will oversee the coordination at the Ann Arbor site working directly with the project manager. For aim 1, Dr. Hawley will direct the RCT, utilizing her experience in conducting large scale RCTs in and outside the VA. She will work with the study co-investigators and site PIs on deployment of the RCT at the 3 sites. Dr. Hawley will oversee the collection of utilization data for Aim 2 and the development of the outcome measures. For aim 3, Dr. Hawley will work with Dr. Damschroder and the other investigators to conduct the process evaluation. For all aims, she will lend HSR/analytic expertise to direct data management and will lead analysis and interpretation of results, with the assistance of Dr. Kim. Dr. Hawley will lead regular meetings with local co-investigators and in-person or video conference meetings with sites on regular intervals (see timeline).

Dr. Hofer will lend his expertise as a primary care physician specifically to the process evaluation component and recommendations for broader scale implementation of the automated telephone system intervention through primary care services. Dr. Hofer will also participate in overall data analysis and interpretation of results.

Dr. Piette will assist with refinement and piloting of survey measures to assess aim 1 outcomes related to implementation of self-management. He will also participate in the evaluation of process evaluation data, and overall data interoperation.

Dr. Skolarus will interact with the site PIs of St. Louis and Pittsburgh regarding clinical issues in deployment of the survey and/or intervention. Dr. Skolarus will lend his prior expertise in development of the automated telephone system prototype intervention to refinement of the tool for this study. He will participate in the aim 3 process evaluating by traveling with Dr. Hawley to St. Louis and Pittsburgh to interview prostate cancer specialists at each site. He will also participate in data analysis and interpretation of results.

Dr. Fagerlin will lend expertise regarding refinement of the automated telephone system tool, focusing on ensuring both are appropriate for Veterans with low literacy levels. She will provide content expertise for the tool regarding how to assess key side effects related to prostate cancer treatment.

Ms. Damschroder will work directly with Dr. Hawley to oversee the process evaluation proposed in this study.

Jordan Sparks (Qualitative Data Analyst). (3 CM Yr 4 only). Ms. Sparks will provide expertise during the final year of the study to conduct the qualitative evaluation of the transcripts obtained from the patient and key stakeholder process evaluation interviews. This person will work under the guidance of Ms. Damschroder under the direction of Dr. Hawley to generate themes and issues from the interviews for review by the study team.

Tabitha Metreger, MA (project manager) This person will coordinate this proposed study, including working with the study team to manage meetings, working with Ms. Davis to direct data management and patient identification needs, and working with Dr. Hawley and the site PIs to oversee the activities of the research coordinators at each site, including data transfers, maintaining follow up records, and initiating contact for the RCT. She will coordinate all IRB submissions for the project, assisting site coordinators as needed.

Jennifer Davis, MHSA (Data manager) The project data manager will use data from the VA Corporate Data Warehouse (CDW) to identify potentially eligible patients. The data manager maintains these files. Survey data will be entered by the coordinator into an ACCESS database stored in an access restricted study folder on a secure server behind the VA firewall. Survey data will be linked to data obtained from the automated telephone system and to utilization data collected from CDW and the National Patient Prosthetics Database (NPPD) from Patient Care Services 12 months following enrollment. All datasets will be stored and merged in an access restricted study folder behind the VA firewall for analysis by VAAAHS study staff.

Leah Gillon (Back-up Data Manager) Ms. Gillon will serve as back-up data manager for the study in the event Ms. Davis is unable to perform her duties. Ms. Gillon may also assist with creation, refinement and maintenance of study ACCESS databases.

Soohyun Hwang (Research Coordinator) This position will pertain to intervention related tasks under the direction of Dr. Hawley and the project manager at the coordinating site (Ms. Metreger). Ms. Hwang's main task during year 1 and into year 2 will be participant recruitment and coordinating and implementing the survey telephone follow-up. After phase 1 is complete, the research coordinator will be responsible for contact of Veterans interested in the RCT, eligibility confirmation, and enrollment into the RCT. She will be responsible for collecting data about those eligible for the RCT and entering it into the CHCR secure website and downloading the IVR data to the study folder behind the VA firewall on a regular basis (to be directed by the Project Manager).

Karen Breisinger (Research Coordinator) This position will pertain to intervention related tasks under the direction of Dr. Gingrich and the project manager at the coordinating site (Ms. Metreger). Ms. Breisinger's main task during year 1 and into year 2 will be participant recruitment and coordinating and implementing the survey telephone follow-up. After phase 1 is complete, the research coordinator will be responsible for contact of Veterans interested in the RCT, eligibility confirmation, and enrollment into the RCT. She will be responsible for collecting data about those eligible for the RCT and entering it into the CHCR secure website and downloading the IVR data to the study folder behind the VA firewall on a regular basis (to be directed by the Project Manager).

Mirela Grabic (Research Coordinator) This position will pertain to intervention related tasks under the direction of Dr. Grubb and the project manager at the coordinating site (Ms. Metreger). Ms. Grabic's main tasks will be participant recruitment and coordinating and implementing the survey telephone follow-up. The research coordinator will be responsible for contact of Veterans interested in the RCT, eligibility confirmation, and enrollment into the RCT. She will be responsible for collecting data about those eligible for the RCT and entering it into the CHCR secure website and downloading the IVR data to the study folder behind the VA firewall on a regular basis (to be directed by the Project Manager).

- **If applicable provide information on any services that will be performed by contractors including what is being contracted out and with whom.**

  Hosting of the IVR system and tailoring for the newsletter will be performed by the University of Michigan's Center for Health Communications Research (CHCR), an NCI-designated Center of Excellence in Cancer Communications Research. This project will benefit from the CHCR-developed Michigan Tailoring System (MTS), an open source technical platform that promotes ease of authoring and dissemination of tailored programs. Information entered into the automated telephone monitoring system by the patient will be merged with basic information obtained about the patient from VA's Patient Care Database and from the baseline survey (specifically name, address, telephone number, age, ethnicity, marital/relationship status, prostate cancer treatment type, initial diagnosis date, service branch VA Site, and PEPPI scores). This information will be entered by project staff into a secure website on a CHCR UM web server that meets all VA criteria for confidential data transfer and is FIPS 140-2 compliant. Collectively, this information will be used to generate an MTS dataset that will be used to generate the newsletters. Newsletters will be 4 to 8 pages in length: untailored newsletters will be 4 pages; the initial tailored newsletter will be 8 pages and all subsequent newsletters will be 4 pages unless patients select a new symptom area to focus on, in which case they will receive another 8 page newsletter. The CHCR team at the University of Michigan will have access to identifiable information; however, we are in the process of obtaining a data use agreement and all CHCR staff assigned to work on this project have completed the WOC process mandatory training including VA Privacy and Information Security Awareness and Rules of Behavior and Privacy and HIPAA Training.

- **If applicable provide information on any Memoranda of Understandings (MOUs) or Data Use Agreements (DUAs) that are being entered into including with whom and for what reason.**

  We have obtained Data Use Agreements between CHCR and VAAAHS, VAPHS and VASTL.

5.0 Study Procedures

5.1 Study Design

- **Describe experimental design of the study. Include sequential and/or parallel phases of the study, including durations, and explain which interventions are standard of care.**

Through a randomized controlled trial, we propose to evaluate the effectiveness of a personally tailored, automated prostate cancer (PC) symptom self-management intervention, compared to enhanced usual care. Participants randomized to the intervention arm will receive automated telephone monitoring and personally tailored newsletters. Participants randomized to the control condition will receive standard care plus information about symptom self-management at the time of enrollment. Participants in both arms will also be asked to complete surveys by phone.

There are three primary Veteran-reported trial outcomes which will be measured at 5- and 12-months post enrollment: 1) confidence in symptom self-management, 2) implementation of symptom self-management, and 3) symptom burden and PC-QOL. Self-efficacy in patient-physician interactions will also be assessed at baseline, 5-months and 12-months. Participants in the trial will be randomized by computer by VA Ann Arbor Healthcare System (VAAAHS) study staff. We hypothesize better outcomes in the intervention arm relative to enhanced usual care. The impact of the intervention on two secondary psychosocial outcomes, overall subjective health and perceptions of cancer control, will be assessed only at the 12-month time point, when we believe the intervention is most likely to have had its impact on these outcomes. The trial will be conducted in four VA sites (Ann Arbor, Cleveland, Pittsburgh, and St. Louis) with a large and racial/ethnically diverse population of PC survivors between 1-10 years post-treatment. The intervention is based on a conceptual framework that describes how self-management contributes to positive outcomes for cancer patients and survivors; we also will utilize theoretical constructs from patient empowerment and cognitive behavioral therapy (CBT) to inform the content of our intervention. We will compare the quality of health care received in intervention and control subjects using guidelines for prostate cancer survivorship care developed by the Michigan Cancer Consortium as a benchmark. Finally, we will prepare for implementation of the intervention on a broader scale through a formative evaluation. This design will allow us to understand how the intervention can best optimize the quality of life and quality of care for Veterans with PC, and will inform how to implement the program more broadly with our primary care partners.

- **Include a description of how anticipated risk will be minimized and include an analysis of risk vs. potential benefit.**

How anticipated risk will be minimized:

Veteran participants:

Psychological: The introductory letter and screening process aren't done by a caregiver, reducing the risk of coercion. Additionally, an opt-out telephone number is provided, and those who do not opt-out will be told they are under no obligation to participate, and their care will not be affected by their decision to participate or not participate, at the beginning of the screening call. (We have chosen an opt-out recruitment procedure as this type of strategy is approved by our local IRB and has worked well in helping projects meet recruitment goals. In a previous 2-site randomized controlled trial aimed at increasing colorectal cancer screening led by the investigator, the opt-out strategy translated into significantly higher rates of enrollment. Recruitment occurred within the primary care clinic at two VA medical centers from February 2009 to June 2011. At Site 1, an opt-in strategy was initially adopted. After nine months, recruitment was modified to an opt-out approach. At Site 2, an opt-out strategy was utilized throughout. At Site 1, during the opt-in period, 756 mailings were sent of which 32 subsequently enrolled into the study (4.2%), compared to 106 of 934 potentially eligible subjects during the opt-out period (11.1%, P <0.001). The enrollment rate at Site 2 (opt-out throughout) was 15% (339/2210). Without modifying Site 1's strategy to an opt-out procedure, the study was in danger of not meeting recruitment goals. Hence, we feel the use of opt-out recruitment procedures should be permitted for studies involving minimal risk.)

Participants will be instructed they are free to skip any survey questions administered by study staff that they would prefer not to answer. However, questions administered by the automated telephone system are not

optional. Participants will be told that they may withdraw from the study at any time without penalty. Consistent with the literature and our team's previous experience providing decision aids to study participants undergoing cancer screening, Veterans tend to respond positively to research that seeks to improve the quality of care via educational materials by asking them about their treatment experiences. However, if a potential study participant verbalizes the need for support or wants further clarification of any issue during the screening call, a study investigator will address the concern in a sensitive and professional manner (i.e., by calling the participant directly and/or recommending follow up with his primary care provider).

Social/legal: we believe that risk of a breach of confidentiality is low. Throughout the study, IRB and HIPPA guidelines will be followed to ensure the privacy and integrity of the information we collect. Any breach will be immediately reported to the PI and the appropriate IRBs. In addition, any complaints/concerns expressed to the study staff by participants, providers, or anyone else affected by this study will be immediately reported to the PI and IRB, as will any unexpected events. To minimize the risk of a breach of confidentiality, we will perform the following steps. First, as soon as the cohort is defined by the data manager, each patient in the cohort will be assigned a unique study ID. We will then create an electronic tracking file on an access-restricted secure drive behind the VA firewall that maps the study participant's identifying information to the study ID. No identifying information will be placed on data collection forms (e.g. surveys). Identifiers of potential recruits and study participants will be maintained to allow for follow-up contacts during the data collection phase. These will be kept in study folders accessible only by study staff and will be destroyed according to VHA Records Control Schedule 10-1 (RCS 10-1) once direction for destruction of research records is published by VHA. Electronic data will be maintained in access-restricted study folders on a secure VA server behind the VA firewall maintained by the Ann Arbor coordinating center. All identifiable data will be kept behind the firewall, with access only available to key study team members. The data manager will be responsible for creating analytic datasets for statisticians and investigators; these datasets will be de-identified per HIPAA guidelines. All resulting research data will be presented in aggregate only. Furthermore, study staff sign a pledge of confidentiality and understand that breach of confidentiality is grounds for dismissal. Study staff are required to complete annual training on privacy and HIPPA, as well as biannual training on human subjects protection.

In order to receive the IVR calls, participants must be willing to have study staff enter their name, address, telephone number, age, ethnicity, marital/relationship status, prostate cancer treatment type, initial diagnosis date, service branch VA Site, and PEPPI scores onto a secure, password-protected website hosted by CHCR at the University of Michigan. The CHCR team at the University of Michigan will have access to this information; however, we are in the process of obtaining revised data use agreements. CHCR has extensive expertise in the protection of personal information and follows strict data security protocols. Also, all CHCR staff assigned to work on this project have completed the WOC process mandatory training including VA Privacy and Information Security Awareness and Rules of Behavior and Privacy and HIPAA Training.

The website used to transfer data to CHCR will be protected by a **Transport Layer Security (TLS) protocol**, ensuring that all data transmissions between a user's browser and the web server are encrypted and are therefore secure. The Transport Layer Security (TLS) protocol in use on the website supports both 128-bit and 256-bit encryption, depending on the user's browser. In addition, FIPS 140-2 validated software, specifically OpenSSL and dm-crypt with a FIPS-mode enabled Linux kernel, will be used to store the encrypted data.
All VHA data and derivative data must be stored in an encrypted partition on the Requestor's or its contractors/subcontractors information system hard drive using **FIPS 140-2 validated software**. (See http://csrc.nist.gov/groups/STM/cmvp/validation.html for a complete list of validated cryptographic modules). The application must be capable of key recovery and a copy of the encryption key(s) must be stored in multiple secure locations. FIPS 140-2 (or current version) compliant / NIST validated encryption will be used to secure VHA data stored on any portable drives, IT components, disks, CD's / DVD's.

Data at CHCR will be stored on web servers running in a virtual server environment. MiServer is a U-M-hosted service maintained on the Ann Arbor campus. MiServer includes safeguards required by HIPAA. These datacenters provide protection from lengthy outages, 24/7 staffing, restricted physical access and disaster recovery, they are backed up automatically onto encrypted tape for recovery and security. All servers and the back end databases are password protected. The server runs Red Hat Enterprise Linux 6-based operating system and security patches and updates are downloaded and installed automatically. The following FIPS validated software will be used:
#1933 Red Hat Enterprise Linux 6.2 dm-crypt Cryptographic Module
#1901 Red Hat Enterprise Linux 6.2 Kernel Crypto API Cryptographic Module
#1792 Red Hat Enterprise Linux 6.2 OpenSSH Server Cryptographic Module
#1758 Red Hat Enterprise Linux 6.2 OpenSSL Cryptographic Module

As listed here:
http://csrc.nist.gov/groups/STM/cmvp/documents/140-1/140val-all.htm

All study data will be stored in a password-protected MySQL database residing on an encrypted volume using the FIPS validated dm-crypt software. Access to the database is restricted to the server. No external access is available. Access to servers by study staff is restricted to a password-protected, TLS-encrypted web console using the FIPS validated OpenSSL software, available at https://pcare.miserver.it.umich.edu/. Access to the web console is logged for auditing purposes. Modification to participant records are also logged. Study data can only be downloaded from the web console by study administrators.

Each server is also protected by firewalls to restrict network access to the server. Workstation computers with server access are configured to require passwords (which adhere to the University of Michigan's Password Policy) in order to log in, wake from sleep, or unlock screen savers.

Data from the CHCR server will be downloaded directly to the access-restricted study folder on the secure VA server behind the VA firewall by research staff. To access and download the data from the CHCR server, research staff will be required to log in with a username and password. Data provided to CCMR researchers through the CHCR server will be in coded form, labeled only with a study ID, and with all personally identifying information removed.

VA employees:
We plan to interview up to 40 key stakeholders (up to 4 PCPs and 4 specialists at each site, plus interviews of stakeholders at the VISN and national level), recruited and interviewed by AAVA project staff. By having Ann Arbor study staff recruit the employees, this will reduce the risk of coercion, as in no instance will the recruiting be done by a supervisor of the participants. This will also reduce the risk of a breach of confidentiality. The same precautions for protecting the audio files and transcripts of Veteran participants will be used for protecting these data from VA employees. Data will be stored in an access-restricted study folder so that minimal Ann Arbor study staff members will have access.

Veteran participants and VA employees:
If a study participant (or potential study participant) is upset regarding a survey question, verbalizes the need for support or wants further clarification of any issue during any study calls with staff, a study investigator will address their concern in a sensitive and professional manner. Any complaints/concerns expressed to the study staff by participants, providers, or anyone else affected by this study will be immediately reported to the PI and IRB, as will any unexpected events. Throughout the study, any breach of IRB or HIPPA guidelines will be immediately reported to the PI and the appropriate IRBs.

Transcription:
Interviews of participants and employees will be transcribed. In the event our in-house transcriptionist is unable to provide timely turnaround on transcription requests, we will utilize the Centralized Transcription Service Program (CTSP) out of the VA Salt Lake City (VASLC). Approved staff from the VASLC will transcribe the study's audio files. The VASLC has a Centralized Transcription Service Program available to VA sites and monitored by their own IRB. The study's audio recordings to be transcribed by VASLC staff will be labeled by the subject's unique alphanumeric code and saved behind the VA Firewall in the study's secure project folder on an AAVA OI&T server. The VASLC transcription staff will be given access to a sub-folder within the study's secure project folder. Approved study staff will place a copy of the audio files in this folder for an approved VASLC transcriptionist to access for the purposes of transcription. The VASLC transcriptionist will transcribe each interview and save the completed transcript in the sub-folder using the same alphanumeric code. No data (audio files, in process transcripts, or completed transcripts) will leave the AAVA's secure research server. As completed transcripts become available, approved study staff will move these files from the transcription sub-folder into another sub-folder that is only accessible to study staff, where they will be stored and accessed for qualitative analyses.

Risk vs. potential benefit:

Veteran participants: Although participants may not receive any direct benefit, the risks to participants are minimal and the benefits are great. We believe that those in the intervention (automated prostate cancer symptom management intervention) are likely to receive some benefit in their overall symptom burden as described in our

Study Aim #1 and associated hypotheses. However, control subjects may also experience some benefit in being more attentive to their symptoms as a result of being enrolled in the study and receiving non-tailored newsletters. Because there has been no research testing this type of intervention in prostate cancer survivors experiencing symptom burden, we cannot be sure that intervention subjects will benefit more than control subjects, and this is the primary aim of this research project. The potential benefit to Veteran cancer survivors overall is extremely great. Understanding more about how a low cost, automated intervention can be used to effectively assist Veterans with symptom burden in managing these symptoms and improving their confidence in symptom management is likely to have a broad impact on the lives of one of the largest populations of Veterans using the VHA. The results from this study may benefit other cancer survivors experiencing symptoms, as this type of intervention may be easily translatable.

VA employees: Although participants may not receive any direct benefit, the risks to participants are minimal and the benefits are great. Data from the process evaluation component of this study will be used to help the study team understand how to best implement and maintain a program to address symptom management in prostate cancer survivors. If effective, the potential benefits to the clinicians who care for these survivors is great, as we expect the program to translate into more efficient use of health services.

- **Provide description of the study population (delineate all categories of subjects – patients, providers, family members, employees, etc.). Include anticipated enrollment numbers**

Veteran participants:

Participants will be selected from CDW who meet the following eligibility criteria:

- Veteran patient at one of the four study sites
- History of treatment for prostate cancer treated by surgery, radiation or androgen deprivation therapy between 1-10 years prior to identification
- Has phone number on file and ability to converse on the telephone in English
- No dementia or other significant mental impairment

A random sample of those identified will be asked to participate. Those who elect to participate, and who have a qualifying Brief Screener score (1 or higher on at least 1 symptom) will be randomized to the study. We estimate as many as 553 - 650 veterans will be randomized. All participants will be 40-80 years old at the time of identification, and all will be male as this is a study of prostate cancer. All participants will have a history of prostate cancer; otherwise we expect the health status of these veterans to be varied.

VA employees:

Up to 40 VA employees will be asked to participate in semi-structured interviews. We plan to interview up to 40 key stakeholders (up to 4 PCPs and 4 specialists at each site, plus interviews of stakeholders at the VISN and national level), recruited and interviewed by AAVA project staff. Recruitment of these individuals is not based on any factor other than their position, so we expect males and females of employment age and with a health status good enough to carry out their job duties.

- **As applicable, provide information on any added protections for vulnerable populations.**

Veteran participants:

This project requires no additional costs to patients and the $10 gift card incentive is small enough so as to not be coercive to participants. In addition, patients are free to withdraw from the study at any time and are free to keep the $10 gift card.

VA Employees:

We plan to interview up to 40 key stakeholders (up to 4 PCPs and 4 specialists at each site, plus interviews of stakeholders at the VISN and national level), recruited and interviewed by AAVA project staff. By having Ann Arbor study staff recruit the employees, this will reduce the risk of coercion, as in no instance will the recruiting be

done by a supervisor of the participants. This will also reduce the risk of a breach of confidentiality. The same precautions for protecting the audio files and transcripts of Veteran participants will be used for protecting data from VA employees. Data will be in access-limited study folders so that minimal Ann Arbor study staff members will have access. All electronic data will be stored on a secure VA server behind the VA firewall.

- **If applicable include information on data and specimen banking.**

  N/A

5.2 Recruitment Methods

- **State how many subjects will be needed.**

Veteran participants:

We estimate as many as 553 - 650 veterans will be randomized.

VA employees:

We plan to interview up to 40 key stakeholders (up to 4 PCPs and 4 specialists at each site, plus interviews of stakeholders at the VISN and national level), recruited and interviewed by AAVA project staff.

- **Describe when, where, how and by whom potential subjects will be identified and recruited.**

RCT:
Recruitment and informed consent. We have been granted a waiver of documentation of informed consent and HIPAA Authorization. Potential participants will be sent an introductory letter and a patient information sheet. The introductory letter will briefly describe the study and include a local or toll free number to call if the patient is not interested in participating or would like more information. After one week, a study coordinator will telephone those Veterans who did not opt-out, and if the patient is interested, the coordinator will ensure the patient is properly informed, obtain verbal informed consent, administer the Brief Screener by phone and determine whether that Veteran meets the criteria of having a clinically meaningful symptom burden score (1 or higher on any one symptom, as a measure of low function or high symptom burden) on at least one item.

For Veterans with significant symptoms, the coordinator will assess interest in participating in the trial, review the patient information sheet and answer any questions. The patient information sheet will clearly state that being in the study means that some Veterans will be enrolled into a program of weekly automated telephone calls plus newsletters while the other group will receive only written information about PC symptom self-management at one time-point. We will make clear that we are studying these methods for helping Veterans with long term PC symptoms and we do not have evidence that one approach is better than the other. The patient information sheet will not state which of these is the “intervention” arm. It will further state that to be in the study requires that the Veteran’s name, address, telephone number, age, ethnicity, marital/relationship status, prostate cancer treatment type, initial diagnosis date, service branch VA Site and survey scores be entered into a secure website to a server that meets all VA criteria for confidential data transfer, but that this will be done by the study coordinator and not by the Veteran himself. Finally, the patient information sheet will inform the participant that he is agreeing to a baseline survey and follow up phone call at 5- and 12-months following enrollment. After each of these three assessments, both intervention and control group patients will be called by the IVR system for standardized administration of the EPIC.

Once the Veteran has been deemed eligible, the information sheet has been reviewed, all questions have been answered, and the patient has verbally consented to participate, the study coordinator will then administer the baseline survey over the telephone. Once a participant has been enrolled into the study, AAVA staff will send a $10 gift card by mail.

Should the phone number or address obtained from CDW turn out to be incorrect or outdated, study staff will check the patient’s medical record for current contact information. In the event a letter is returned to us in the mail and an updated address is not available, study staff will attempt to contact the patient by phone up to 3 times including

leaving messages. If the patient is agreeable, study staff will send the recruitment letter to the patient's updated address and contact the patient again after one week to complete the recruitment call as described above.

Process Evaluation:
At the end of the intervention delivery phase, the research team will conduct semi-structured interviews with up to 40 key stakeholders (up to 4 PCPs and 4 specialists at each site, plus interviews of stakeholders at the VISN and national level). Drs. Hawley and Skolarus will arrange interviews with up to 4 PCPs at each site (with the support of the primary care service director) and 4 specialists providing PC survivorship care per site. Recruitment of these individuals will be done via email and phone, with introductory letters sent by Dr. Hawley and the site PIs. Guided interviews will be conducted with these physicians in person or by telephone to assess perceptions of system factors contributing to positive intervention outcomes, and will be audiotaped with their verbal consent.

To identify participant factors influencing intervention effectiveness, we will re-contact participants in the intervention arm who achieved the best outcomes (i.e., had the highest reduction in symptom burden over the study period) and the worst outcomes (i.e., no change in symptom burden or increase in symptom burden). Starting in month 9 of year 3, we will contact 5 participants at each site in the best outcome group, and 5 participants per site in the worst outcome group (N=40 total), based on preliminary data analyses available at that time. We will conduct in-depth interviews with these participants by telephone to determine patient perceptions and factors associated with the intervention's effectiveness. Participants in these interviews will be limited to patients who agreed to this interview during the 12-month follow-up survey. We will initiate re-contact during month 9 of year 3, and continue into months 1-2 of year 4. Telephone interviews are expected to take 30-40 minutes and will be audiotaped with the participants' verbal consent.

- **Describe materials that will be used to recruit subjects, e.g., advertisements. Include materials as an appendix or separate attachment.**

Potential participants will be sent an introductory letter and a patient information sheet. The letter will describe the study and include either a toll-free or local number to call if the patient is not interested in participating or would like more information.

- **Describe any payments to subjects, including the amount, timing (at the end of the study or pro-rated for partial study participation), method (e.g., cash, check, gift card), and whether subjects will experience a delay in receiving the payment.**

Once a participant has been enrolled into the study, AAVA staff will send a $10 gift card by mail. Those patients participating in the evaluation process will receive an additional $20 to compensate them for the 30-40 minutes required for the interview. Payments will not be pro-rated as all payments for this project are minimal and made on a one-time basis. Payment for the ~40 patients participating in the process evaluation interviews will also be in the form of a gift card and will be sent by the AAVA project staff once the interview has been completed.

5.3 Informed Consent Procedures

- **Indicate if informed consent will be obtained and/or if you are requesting a waiver of informed consent or waiver of documentation of informed consent. If the research involves multiple phases, specify for which phases of the research the waiver(s) is being requested and/or the informed consent will be sought.**

Describe who will be obtaining informed consent, if applicable, and any circumstances that may need to be addressed (e.g. subjects with impaired decision making ability and the use of a legally authorized representative, etc.)

We have obtained a waiver of documentation of informed consent and HIPAA authorization for the entirety of the study. Study staff will obtain verbal informed consent during the initial screening call (see patient recruitment script). Generally, the local coordinator will be responsible for recruitment of patients from her own site; however, we plan to add an additional coordinator at the coordinating center (VAAAHS) who will be responsible for assisting with patient

recruitment at all three sites. Also, coordinators from all three sites may assist with recruitment at other sites in cases when a coordinator position is unfilled or due to extended leave.

- **If applicable, indicate how local site study personnel will be trained regarding human subjects protections requirements and how to obtain and document informed consent.**

Study staff sign a pledge of confidentiality and understand that breach of confidentiality is grounds for dismissal. Study staff are required to complete annual training on privacy and HIPPA, as well as biannual training on human subjects protection. We have obtained a waiver of documentation of informed consent and HIPAA authorization for the entirety of the study.

5.4 Inclusion/Exclusion Criteria

- **Describe the criteria that determine who will be included in or excluded from the study.**

Veteran participants:
Participants will be selected from CDW who meet the following eligibility criteria:

- Veteran patient at one of the four study sites
- History of treatment for prostate cancer treated by surgery, radiation or androgen deprivation therapy between 1-10 years prior to identification
- Has phone number on file and ability to converse on the telephone in English
- No dementia or other significant mental impairment

A random sample of those identified will be asked to participate. Those who elect to participate, and who have a qualifying Brief Screener score (1 or higher on at least 1 symptom) will be randomized to the study. We estimate as many as 553 - 650 veterans will be randomized. All participants will be 40-80 years old at the time of identification, and all will be male as this is a study of prostate cancer; otherwise we expect the health status of these veterans to be varied.

5.5 Study Evaluations

- **Describe all evaluations to be conducted (including screening; tests/questionnaires that will be administered; any procedures that subjects will be required to complete) and data collection methods. Include materials as an appendix or separate attachment.**

Potential participants will be sent an introductory packet from the AAVA. After one week, the coordinator will telephone those Veterans who did not op-out, and if the patient is interested, the coordinator will administer the Brief Screener by phone and determine whether that Veteran meets the criteria of having a clinically meaningful symptom burden score (1 or higher on any one symptom, as a measure of low function or high symptom burden) on at least one item. Once the Veteran has been deemed eligible and the baseline survey has been administered, the veteran will be randomized to the automated telephone system or enhanced usual care (information about self-management).

Veterans randomized to the automated telephone system intervention will receive 4 automated phone calls over a 3-month period: 1 at study start and then once a month for 3 months. These calls will last approximately 15 minutes and will include questions about symptoms, will allow the veteran to identify a goal to work on, and help the veteran take steps towards reaching their goal and managing their symptoms. At the end of each call, the veteran will also have the option of listening to an audio testimonial tailored on priority symptom area. Following each call, the veteran will receive a personalized newsletter that will provide more details regarding their symptoms and strategies to help them manage their symptoms. Each newsletter will be 4 – 8 pages in length. The automated system will try to reach the veteran up to eight times over the course of 4 days (see IVR call schedule). If the veteran has not completed the call by day 3 of the call window, study staff will make up to 5 or 6 attempts to contact the patient (including leaving messages) to verify the phone number and preferred call time. If the veteran has still not completed the call by day 5 of the call window, study staff will again make up to 5 or 6 attempts to contact the patient. Following each reminder call, study staff have the option to initiate additional IVR calls should veteran be agreeable.

Veterans randomized to this group may also be contacted to participate in a 30 to 40-minute audio-recorded phone interview to find out about their experience with the program. These interviews will be conducted by the research staff at the Ann Arbor VA in Ann Arbor, MI. During the 12-month survey, veterans will be asked if they are interested in participating in the interview.

Veterans randomized to the control group will receive one 4-page newsletter with educational information about symptoms and symptom management, and will complete a survey over the phone at enrollment and at 5 and 12 months after starting the study.

Telephone surveys of both intervention and control groups to obtain baseline and follow-up measures will be conducted at three time points: baseline, five months, and 12 months post-enrollment. Hard copies of follow-up surveys will be sent to any participants expressing preference for completing the survey by paper and participants we are unable to reach by phone. Survey content will be finalized by our study team using established approaches during year 1 and pilot tested among prostate cancer survivors affiliated with the VAAAHS prior to use in the trial. Each survey will be administered by the VA coordinator over the telephone. After each of these three assessments, both intervention and control group patients will be called by the IVR system for standardized administration of the EPIC. Baseline surveys will be done prior to randomization. Beginning approximately 4 months following enrollment, initial attempts will be made by the coordinating team to contact the participant by phone to complete the Time 2 survey, and approximately 11 months following enrollment to complete the Time 3 survey. For all 3 surveys, up to 5 or 6 attempts will be made to complete the survey, including leaving voice mails and providing call-back information for participants who are not home. Times to complete the surveys will be scheduled as desired by participants. Finally, if participants are unable or unwilling to complete the survey by telephone, a paper-and-pencil survey will be mailed to them with a return envelope. Participants who fail to return the paper survey within one month may be sent a second paper survey by mail. In addition, a reminder newsletter will be sent to participants 1-2 months prior to their expected 12-month follow-up. All participants completing the 12-month assessment will be sent an “early results” newsletter showing some preliminary survey results and thanking participants for their contribution to the study.

Patients are free to skip any survey questions administered by study staff that they would prefer not to answer. However, because the newsletters are tailored based on responses to questions administered by the automated telephone system, these questions are not optional. Nevertheless, patients are free to hang up the phone if they prefer not to complete an IVR call. Patients will also have the option to call into the IVR system using a toll free number if they prefer not to wait to complete their call.

We will use the Expanded Prostate Cancer Index (EPIC) to assess PC-symptom burden and associated PC-QOL at the baseline, 5- and 12-month assessments. The EPIC was developed by our study consultant, Dr. Wei, and has been widely used in prostate cancer survivorship research. The EPIC is a 26-item measure that assesses symptom burden in four domains: urinary symptoms (9 items), bowel symptoms (6 items), sexual symptoms (6 items) and vitality (5 items). Each domain has a subscale related to function and bother which together contribute to disease specific quality of life. Prior work by Dr. Wei and colleagues has shown that these domains have good internal consistency (Chronbach’s alpha > 0.82 for each domain) and correlate highly with other established measures of QOL.107 Each domain has a range of possible scores from 0 to 100, with lower scores indicating worse symptom burden. Lower EPIC scores for any one domain are associated with lower function in that domain (e.g., lower sexual health function) and lower QOL. Thus higher symptom burden, which reflects both function and bother scores, translate into lower EPIC scores. Based on consultation with Dr. Wei and on prior work by his team, for purposes of this study we will consider a score of 70 or less to indicate “clinically meaningful symptom burden” for any one domain. We will conduct primary outcome analyses using the EPIC. Self-efficacy in patient-physician interactions will also be assessed both at baseline and 12-months using a 5-item short form version of the Perceived Efficacy in Patient-Physician Interactions (PEPPI). The PEPPI was developed to measure older patients' self-efficacy in obtaining medical information and attention to their medical concerns from physicians. PEPPI has good convergent and discriminant validity and strong reliability (α=0.93).

At the 12-month assessment we will evaluate two key psychosocial domains of QOL (subjective health and perceptions of cancer control) that have been shown to be impacted by PC treatment in prior research. We will assess subjective health using the VR-12, an established measure of overall QOL that includes perceptions of one’s health. We will assess perceived cancer control using a measure developed in prior research examining the psychosocial impact of prostate cancer; this measure includes three domains related to confidence that one’s cancer is under control, worries about recurrence, and appraisals of one’s coping with prostate cancer. We will evaluate these

outcomes at the 12-month assessment because that is when we expect the intervention would have its largest impact on these psychosocial domains of QOL.

The primary outcome for Specific Aim 2 will be use of VA services related to prostate cancer survivorship care at the 12 month assessment point. We will use the 12 month assessment point to ensure we capture any medication or service use related to prostate cancer symptom management that may occur after patients' exposure to the intervention has ended. Because there are no VA guidelines for appropriate management of prostate cancer survivors, we also will operationalize symptom-specific utilization consistent with MCC guidelines which are expert and evidence based. In the absence of VA guidelines for prostate cancer survivorship care, we considered national, regional and specialty organization guidelines. While there exists considerable overlap in recommendations, we ultimately chose the Michigan Cancer Consortium (MCC) guidelines for prostate cancer survivorship care as a standard against which to assess self-management approaches as well as use of services. We chose the MCC guidelines because they have good coverage of symptom management, the consortium is based in the same geographic area as our study sites, and because 2 study co-investigators contributed to their content (Skolarus, Wei). We will operationalize utilization consistent with these guidelines using criteria mapping. This process has been used extensively to develop sets of quality metrics using a set of recommendations, when evidence-based guidelines do not exist, as is the case with prostate cancer survivorship care. Specifically, for each symptom indicated by the participant at baseline, we will determine potentially appropriate use of services by mapping receipt of services at the 12 month assessment to those outlined in the MCC recommendations. For analysis purposes, we will consider care recommended by the MCC as "guideline-concordant" even though the MCC are not fully evidence based guidelines. Data will be derived from three sources described in the Analytic Plan section below. For instance, if the patient indicates a problem with sexual function at baseline, we will measure use of pharmacologic treatments such as the phosphodiesterase inhibitors (sildenafil, tadalafil, vardenafil) or prostaglandin E1 (alprostadil as injection or intraurethral pellet), use of medical devices such as a vacuum erection device, a visit to a urologist, or receipt of surgery such as a penile prosthesis. Pharmacological agents for managing problems with urination include oxybutynin (Ditropan), tolterodine (Detrol) and phenazopyridine. Global measures for each symptom will indicate use of any of the pharmacologic, device, or referral measures suggested in the guideline. We also will create continuous measures of guideline-concordance service use from zero (none of the non-self-management approaches used in the prior year) to the maximum number of options for that specific symptom. Switching from one pharmacologic approach to another will be counted as separate approaches. The outcomes for Aim 2 (use of prostate cancer survivorship services consistent with those recommended by the MCC) will be obtained from two sources. We will collect pharmacy data, patient demographics, diagnoses, the date and type of utilization events, location of services (study site as well as clinic type), and the patients' assigned primary care provider from the Corporate Data Warehouse (CDW). To obtain information about device utilization, such as a penile clamp for incontinence control, we will use both CDW and the National Patient Prosthetics Database (NPPD) from Patient Care Services. Having the CDW and the NPPD records will ensure we can collect the most accurate device utilization. The process for requesting a data extract from these sources will be initiated at the end of year 2, to ensure sufficient time to obtain appropriate approvals for these datasets to be accessed by the data analyst from the AAVAHS.

We will collect information about participants' use of primary and specialty care from VA records in the 12 months between study enrollment and the final assessment. To account for services potentially received outside of the VA, we will ask participants at both the 5- and 12-month assessments to report the number of times over the prior interval that they visited their VA primary care physician and a specialist (urologist, oncologist, radiation oncologist, or gastroenterologist). For each visit, we will ask them to indicate whether the visit was related to their prostate cancer symptom management. We will also use the datasets created through Aim 2 to assess patients' use of primary and/or specialty care 12-months post enrollment.

5.6 Data Analysis

- **Provide sample size determination and analysis (include anticipated rate of screen failures, study discontinuations, lost to follow-up etc.).**

In a recent EPIC study, the minimal clinically important difference for the four EPIC domains was defined as the difference in scores between patients who were completely satisfied with their symptom burden (function and bother combined) versus only somewhat satisfied. Minimally important differences ranged from 0.33 standard deviation (SD) to 0.5 SD, which translated into a difference of six points for urinary incontinency scores, four points for bowel, 10 points for sexual function, and 4 points for hormonal symptoms. In the proposed study, we consider these differences as the clinically meaningful between-group mean difference in symptom reduction. To detect a 0.33 SD difference in symptom reduction between patients receiving the automated PC symptom support versus standard information at 12

month with 90% power, we will need 394 participants (197 per group), based on using a regression analysis adjusting for baseline values (analysis of covariance) with an α of 0.0125 with 0.5 as an assumed correlation between baseline and follow-up symptom scores. Note that the α value was chosen conservatively to detect symptom reduction in any of the four domains. The power will be higher to detect a larger than 0.33 SD between-group difference in symptom reduction and also to detect the same difference with higher correlation than 0.5 between baseline and follow-up symptom values. Assuming conservatively 15% attrition at each assessment time, we propose to enroll 550 participants in total with an anticipated 397participants to complete assessments at the second assessment time. The number of eligible prostate cancer patients at each site is sufficient for recruitment. For interval scale outcomes measures such as confidence in symptom self-management, the proposed sample size should give adequate power to detect at least 0.33 SD differences between groups.

- **Describe how, where and by whom the data will be analyzed.**

All data will be analyzed at the Ann Arbor VA. The qualitative data analyst, Jordan Sparks, the data manager, Jennifer Davis, and Drs. Hawley, Hofer and Piette will participate in the data analysis.

Aim 1 initial analyses and data verification: Analyses will be done in three phases. Baseline analysis (data verification) will include examining the distribution of all study variables to assess extreme values, missing data, variances, skewness, and type of distribution. Descriptive statistics will be used to describe the distribution of baseline variables in the two groups. We will use means, medians, and ranges for continuous variables such as age and baseline symptom scores, and we will use proportions for discrete variables. Baseline comparability of the two groups will be assessed using two-group t-tests for continuous variables, and chi-square tests for dichotomous or categorical variables. Variables found to be associated with the study groups will be included in subsequent analyses as covariates to adjust for potential differences between groups, and the results will be interpreted with any baseline imbalances in mind. We also will evaluate bivariate associations between patients' experimental condition and the outcomes, as well as between each covariate and the outcomes and between each covariate and group assignment. These analyses will be done to determine unadjusted measures of effect, assess possible confounders, and anticipate any collinearity in subsequent analyses. We will also report by study group the percent of patients who reached EPIC symptom scores above 70 (i.e., "better symptom burden") at both 5- and 12- months. In the final phase we will use multivariable models to estimate the intervention effect. We will conduct graphical analysis to explore variation in outcome variables over time and between the two experimental groups. We will evaluate the trends in symptom burden, knowledge and information need over time in the two study groups separately. Results of these graphical analyses will be used to fine-tune the analytic course described below.

Aim 1 outcome analyses: Our primary outcomes for Aim 1 will be changes in symptom burden and bother scores at 5-months relative to baseline, using the EPIC measure. We will also evaluate these outcomes at the 12-month assessment point, but focus on the 5-month for primary outcome assessment as it is closest to the completion of the intervention. Multiple regression analysis will be used to evaluate the primary outcomes. The model will include an indicator for intervention group as the primary independent variable, and treatment type indicator (surgery vs. radiotherapy) and study site indicators as covariates. Baseline variables found to differ between the two study groups in the baseline analysis will also be included as covariates, though we expect the groups to be balanced on demographic and symptom scores by the randomization process. The coefficient for the intervention group indicator will be used to evaluate the impact of the personalized automated prostate cancer symptom management program compared to standard information. For change in symptom burden, we will repeat the analysis using each of the four symptom domains for EPIC. We will use the same analytic approach to evaluate changes in confidence in symptom self-management, our second Aim 1 outcome. We hypothesize that for both Aim 1 outcomes, intervention group survivors will have better scores at both 5-and 12-month assessments relative to those in the group (i.e., less symptom burden and better PC-QOL, more confidence in symptom self-management). For patients with available data at both 5- and 12-months, we will assess the trajectory of symptoms over time. This will be done using a linear mixed-effects model with random effects for each subject, an indicator for intervention group, an indicator of follow-up wave (5 versus 12 months) and an interaction of time by intervention group to model potential changes in the intervention effect on symptoms soon (at 5-months) vs. long (at 12-months) after the intervention is discontinued. If the interaction is not significant, we will drop the interaction term from the model and estimate the time-averaged difference in outcomes between the two study groups. Analyses of other outcomes, such as self-management implementation and confidence, will be done similarly.

Aim 2 Analysis: For Aim 2, we hypothesize that 12 months after enrollment, Veterans in the automated prostate cancer symptom management intervention will have higher rates of use for PC survivorship services that are consistent with the recommendations of the MCC than control patients. The primary outcome for Specific Aim 2 will be use of symptom-specific MCC guideline-concordant care assessed at 12 months. Using our global measure of use of any symptom-specific guideline concordant care (yes/no), we will evaluate differences across intervention conditions

using a logistic regression model including all participants and controlling for potential baseline confounders. We will then conduct additional logistic analysis within subgroups of patients with various symptom patterns at baseline. For these models, the primary outcome will be use of guideline-concordant care for a specific symptom (yes/no). Secondary independent variables will include the EPIC baseline score. We will control for Veteran demographics (including age, race/ethnicity, education and income), study site, and type of treatment received (i.e., radiation versus chemotherapy). We will then explore the total amount of guideline concordant services received in regression models appropriate for skewed count data (e.g., poisson or negative binomial models).

5.7 Withdrawal of Subjects

- **Describe any anticipated circumstances under which subjects will be withdrawn from the research without their consent.**

There are no anticipated circumstances under which subjects will be withdrawn without their consent.

- **Describe the consequences of a subject's decision to withdraw from the research and the procedures for orderly termination of participation by the subject (e.g., the subject contacting the investigator for an end-of-study visit).**

This is an RCT but as will be clear in the information letter, patients may choose to withdraw from the study at any time. If IVR calls are not answered, study staff will attempt to contact patients (up to 5 or 6 attempts will be made, including leaving voice mails and providing call-back information for participants who are not home) to determine whether they wish to continue participating. Participants who indicate they have changed their mind and no longer wish to continue in the study will not be contacted again.

6.0 Reporting

- **Include procedures for reporting unanticipated problems, serious adverse events, and protocol deviations.**

Reports of related SAEs and UAPs and protocol deviations will be made by the study team member who discovers the event, the site coordinator, or the project manager to the VA Central IRB (CIRB). The Ann Arbor project manager should be notified at the same time a report is made if the report is coming from another site's study team member. Any unanticipated related incidents involving a death at any of the 3 study sites will be reported immediately to the CIRB. Any unanticipated related incidents involving SAEs and UAPs meeting the definition of serious will be reported within 5 business days of discovery to the CIRB secure SharePoint site dedicated to this purpose. AEs and UAPs that are not related are to be reported to Ann Arbor project manager as they are discovered, and will be reported to the CIRB in summary at the time of continuing review/project closure. Protocol deviations/violations that are likely to substantially adversely affect 1) the rights, safety, or welfare of a participant; 2) a participant's willingness to continue participation; or 3) the integrity of the research data, including VA information security requirements will all be reported within 5 working days of being made aware of the occurrence. These will be reported through the secure SharePoint site dedicated to this purpose.

It is possible the automated system and follow-up surveys may uncover certain symptoms that warrant medical attention. The 2 possible symptoms that the automated system could uncover is blood in stools and/or urine, though the likelihood of either of these is low. If a study participant reports blood in stool and/or urine (or other concerning symptoms requiring the input of a physician), study staff will contact the participant to confirm the report. For all participants verifying current or recent symptoms, we will enter a progress note in the patient's medical chart with a description of the patient's reported symptoms and a request for follow-up and add the appropriate provider(s) as additional signers on the note. This plan has been reviewed and approved by all the MDs on the study. In the event a study participant has no assigned provider(s) at the VA appropriate for follow up of reported concerning symptoms, study staff will contact the participant directly and encourage him to notify his primary care (or other) provider of said symptoms. Should the study participant express concerns or request additional information, or in the event the participant has no assigned community-based provider, the patient will be contacted by a study MD. In the event we

are unable to reach participants by phone who have no VA assigned provider, study staff will send a letter by mail encouraging them to notify their provider of the reported symptoms.

Complaints from participants regarding VA medical care unrelated to the study should be documented by study staff and reported to the local Patient Advocate Liaison.

7.0 Privacy and Confidentiality

- **Describe whether the study will use or disclose subjects' Protected Health Information (PHI).**

The project data manager will use data from the VA Corporate Data Warehouse (CDW) to identify potentially eligible patients. The data manager maintains these files.

Potential participants will be sent an introductory packet from the AAVA. After one week, the coordinator will telephone those Veterans who did not op-out, and if the patient is interested, the coordinator will administer the Brief Screener by phone and determine whether that Veteran meets the criteria of having a clinically meaningful symptom burden score (1 or higher on any one symptom, as a measure of low function or high symptom burden) on at least one item.

Once the Veteran has been deemed eligible, the information sheet has been reviewed, all questions have been answered, and the patient has verbally consented to participate, the study coordinator will then administer the baseline survey over the telephone.

Survey data will be entered by the coordinator into an ACCESS database stored in an access-restricted study folder on a secure server behind the VA firewall. Survey data will be linked through study ID to data obtained from the automated telephone system and to utilization data collected from administrative databases 12 months following enrollment. All datasets will be stored and merged in an access-restricted study folder behind the VA firewall for analysis by VAAAHS study staff.

- **Describe the steps that will be taken to secure the data (e.g., training, authorization of access, password protection, encryption, physical controls, Certificates of Confidentiality, and separation of identifiers and data)**

All paper records will be kept in locked offices in locked file cabinets in VA offices. Access to the file cabinets will be restricted to research personnel. All electronic data will be kept secured on VA servers behind the VA firewall. No data will be stored on computer hard drives.

To minimize the risk of a breach of confidentiality, we will perform the following steps. First, as soon as the cohort is defined by the data manager, each patient in the cohort will be assigned a unique study ID. We will then create an electronic tracking file on an access-restricted secure drive that maps the study participant's identifying information to the study ID. No identifying information will be placed on data collection forms (e.g. surveys). Identifiers of potential recruits and study participants will be maintained to allow for follow-up contacts during the data collection phase. These will be kept in study folders accessible only by study staff and will be destroyed according to VHA Records Control Schedule 10-1 (RCS 10-1) once direction for destruction of research records is published by VHA. Electronic data will be maintained behind the secure VA firewall and maintained by the Ann Arbor coordinating center. All identifiable data will be kept behind the firewall, with access only available to key study team members. The data manager will be responsible for creating analytic datasets for statisticians and investigators; these datasets will be de-identified per HIPAA guidelines. All resulting research data will be presented in aggregate only. Furthermore, study staff sign a pledge of confidentiality and understand that breach of confidentiality is grounds for dismissal. Study staff are required to complete annual training on privacy and HIPPA, as well as biannual training on human subjects protection.

Information entered into the automated telephone monitoring system by the patient will be merged with basic information obtained about the patient from VA's Patient Care Database and from the baseline survey (specifically name, address, telephone number, age, ethnicity, marital/relationship status, prostate cancer treatment type, time since treatment, service branch and survey scores). This information will be entered by project staff into a secure

website to a CHCR UM server that meets all VA criteria for confidential data transfer. Collectively, this information will be used to generate an MTS dataset that will be used to generate the newsletters. The CHCR team assigned to work on this project will have access to identifiable information; however, we are in the process of obtaining a data use agreement. Also, CHCR staff working on this project have completed the WOC process mandatory training including VA Privacy and Information Security Awareness and Rules of Behavior and Privacy and HIPAA Training.

The website used to transfer data to CHCR will be protected by a **Transport Layer Security (TLS) protocol**, ensuring that all data transmissions between a user's browser and the web server are encrypted and are therefore secure. The Transport Layer Security (TLS) protocol in use on the website supports both 128-bit and 256-bit encryption, depending on the user's browser. In addition, FIPS 140-2 validated software, specifically OpenSSL and dm-crypt with a FIPS-mode enabled Linux kernel, will be used to store the encrypted data. All VHA data and derivative data must be stored in an encrypted partition on the Requestor's or its contractors/subcontractors information system hard drive using **FIPS 140-2 validated software**. (See http://csrc.nist.gov/groups/STM/cmvp/validation.html for a complete list of validated cryptographic modules). The application must be capable of key recovery and a copy of the encryption key(s) must be stored in multiple secure locations. FIPS 140-2 (or current version) compliant / NIST validated encryption will be used to secure VHA data stored on any portable drives, IT components, disks, CD's / DVD's.

Data at CHCR will be stored on web servers running in a virtual server environment. MiServer is a U-M-hosted service maintained on the Ann Arbor campus. MiServer includes safeguards required by HIPAA. These datacenters provide protection from lengthy outages, 24/7 staffing, restricted physical access and disaster recovery, they are backed up automatically onto encrypted tape for recovery and security. All servers and the back end databases are password protected. The server runs Red Hat Enterprise Linux 6-based operating system and security patches and updates are downloaded and installed automatically. The following FIPS validated software will be used:
#1933 Red Hat Enterprise Linux 6.2 dm-crypt Cryptographic Module
#1901 Red Hat Enterprise Linux 6.2 Kernel Crypto API Cryptographic Module
#1792 Red Hat Enterprise Linux 6.2 OpenSSH Server Cryptographic Module
#1758 Red Hat Enterprise Linux 6.2 OpenSSL Cryptographic Module
As listed here:
http://csrc.nist.gov/groups/STM/cmvp/documents/140-1/140val-all.htm

All study data will be stored in a password-protected MySQL database residing on an encrypted volume using the FIPS validated dm-crypt software. Access to the database is restricted to the server. No external access is available. Access to servers by study staff is restricted to a password-protected, TLS-encrypted web console using the FIPS validated OpenSSL software, available at https://pcare.miserver.it.umich.edu/. Access to the web console is logged for auditing purposes. Modification to participant records are also logged. Study data can only be downloaded from the web console by study administrators.

Each server is also protected by firewalls to restrict network access to the server. Workstation computers with server access are configured to require passwords (which adhere to the University of Michigan's Password Policy) in order to log in, wake from sleep, or unlock screen savers.

Data are provided to researchers in coded form, with all personally identifying information removed. Upon study completion, CHCR will delete all participant data (as will be described in the DUA) and all data stored on VA servers will be permanently de-identified for archive and then destroyed according to VHA Records Control Schedule 10-1 (RCS 10-1) once direction for destruction of research records is published by VHA.

8.0 Communication Plan

- **Include plan for ensuring all required local site approvals are obtained and notifying the Director of any facility where the research in being conducted but the facility is not engaged.**

The project manager will verify VA Central IRB approval and the local VA facility approval before study recruitment can begin at that site. There are no facilities where the research is being conducted but the facility is not engaged in research.

- **Include plan for keeping all engaged sites informed of changes to the protocol, informed consent, and HIPAA authorization**

As this project is being implemented, the research team will conduct regular conference calls (approximately weekly) with the implementation team at each site, to track progress and address any questions that arise regarding implementation. These weekly calls will continue for the first few months of patient enrollment and will decrease in frequency as appropriate, depending on the challenges (or lack thereof) associated with implementation.

- **Include plan for informing local sites of any Serious Adverse Events, Unanticipated Problems, or interim results that may impact conduct of the study.**

Reports of related SAEs and UAPs and protocol deviations will be made by the study team member who discovers the event, the site coordinator, or the project manager to the VA Central IRB (CIRB). The Ann Arbor project manager should be notified at the same time a report is made if the report is coming from another site's study team member. Any unanticipated related incidents involving a death at any of the 4 study sites will be reported immediately to the CIRB. Any unanticipated related incidents involving SAEs and UAPs meeting the definition of serious will be reported within 5 business days of discovery to the CIRB secure SharePoint site dedicated to this purpose. AEs and UAPs that are not related are to be reported to Ann Arbor project manager as they are discovered, and will be reported to the CIRB in summary at the time of continuing review/project closure. Protocol deviations/violations that are likely to substantially adversely affect 1) the rights, safety, or welfare of a participant; 2) a participant's willingness to continue participation; or 3) the integrity of the research data, including VA information security requirements will all be reported within 5 working days of being made aware of the occurrence. These will be reported through the secure SharePoint site dedicated to this purpose.

- **Include plan for ensuring the study is conducted according to the IRB-approved protocol.**

The regular calls mentioned above will be used as opportunities to ensure the study is conducted according to the IRB-approved protocol. These team calls will include discussion of any updates to the protocol, recruitment procedures, and any issues (i.e. SAEs, UAPs, and protocol deviations, etc) that arise during the course of the study. Minutes for these meetings, and any updated documentation, will be posted to the AAVA study drive, to which study staff will have access.

- **Include plan for notifying all local facility directors and LSIs when a multi-site study reaches the point that it no longer requires engagement of the local facility (e.g., all subsequent follow-up of subjects will be performed by the PI from another facility).**

At the end of any individual site's participation in this research, the local facility director and LSI will be notified by an email from an Ann Arbor study investigator.

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