Study Title: De-implementation of Low Value Castration of Men With Prostate Cancer (DeADT)

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NCT: NCT03579680

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PREFACE

This document describes the elements required for a simple minimal risk research protocol. Minimal risk studies may require more elements and oversight structure if the complexity or size of the study adds additional importance.

*"**Minimal risk** means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." See the Common Rule at* http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.102.

Further Guidance on what categories of research would meet minimal risk definition can be found at http://www.hhs.gov/ohrp/humansubjects/guidance/expedited98.htm .

Minimal Risk studies, while simpler than studies of greater than minimal risk, still have regulatory obligations. A well written protocol is the prologue to well conducted research and as such, a minimal risk protocol should include, at a minimum, sections on brief background/rationale, study objectives, expected risks/benefits, eligibility, subject enrollment, study design/procedures, data collection and management, data analysis, quality control and quality assurance, statistical considerations, informed consent, privacy issues, unanticipated problems, and references. The following pages describe a template suitable for use. It is anticipated that the average minimal risk study can be described in less than 10 pages using this template. A few thoughtful sentences in each section are preferred to large chunks of information cut-and-pasted from other documents.

A grant application is not acceptable as a protocol.

Title

De-implementation of low value castration for men with prostate cancer (DeADT)

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Protocol Amendments:
Updating application from a Project Lacking Immediate Plans for Involvement of Human Subjects to an application for research involving human subjects.

- Adding Co-Investigators (Section 1.3)
- Adding VA Ann Arbor Healthcare System as a performance site (Section 3)
- Revising study activities (Section 3.1)

Version 0.3

March 26, 2019

Version 0.4

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SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations.

Site Investigator:*

Signed:  Date: 3/26/19

Name: Ted Skolarus, MD
Title: Principal Investigator

** The protocol should be signed by the clinical site investigator who is responsible for the day to day study implementation at his/her specific clinical site.*

LIST OF ABBREVIATIONS

AAVA	VA Ann Arbor Healthcare System
ADT	androgen deprivation therapy
CCMR	VA Center for Clinical Management Research
CDW	VA Corporate Data Warehouse
Co-I	Co-Investigator
DCE	discrete choice experiments
HIPAA	Health Insurance Portability and Accountability Act
HSR&D	VA Health Services Research & Development
PC	Prostate Cancer
PHI	protected health information
RA	Research Assistant
TACT	target, action, context, time
TDF	Theoretical Domains Framework
TIDieR	Template for Intervention Description & Replication
VA	Veterans Affairs
VIReC	VA Information Resource Center
VREC	Veteran Research Engagement Council

1 BACKGROUND/SCIENTIFIC RATIONALE

A. BACKGROUND & SIGNIFICANCE

A1. Evidence for castration as prostate cancer treatment

Because prostate cancer cells are dependent on androgens, i.e., testosterone, depriving them of this hormone through castration can improve clinical outcomes, for some patients.[1] The highest levels of evidence for chemical castration with androgen deprivation therapy (ADT) injections to treat prostate cancer occur in two scenarios: 1) high risk localized disease in combination with radiation therapy, and 2) metastatic cancer with spread to bones or other organs causing symptoms.[2-4] However, a significant amount of castration in Medicare and integrated delivery systems (e.g., VA), occurs outside scenarios where high levels of benefit exist.[5,6] For example, using castration for the primary treatment of localized prostate cancer is likely ineffective and harmful, yet remains common in VA with five-fold variation across facilities (Figure 1). Neither long-term studies nor current guidelines support castration as primary treatment for localized prostate cancer.[1,3,4] Many times, this castration is continued indefinitely. Even in cases of metastatic prostate cancer without symptoms, an American Society of Clinical Oncology Panel could not make a recommendation for treatment with ADT until symptoms of disease progression (e.g., bone pain) occur due to a lack of an overall survival advantage for those treated early.[7]

A2. There is a disconnect between the value and use of castration in prostate cancer

A2.1 Surgery to remove testicles is no longer needed for castration

The discovery that castration could be used as palliation for patients with metastatic prostate cancer revolutionized the oncology field in 1941.[8] Depriving prostate cancer cells of testosterone to relieve urinary tract blockage and decrease bone pain from metastatic lesions ushered in a new way to think about treating the disease that continues to fuel treatment approaches today. However, surgical castration via orchiectomy (i.e., testicular removal) fell by the wayside in the 1990s as long-acting injectable approaches to androgen deprivation (GnRH agonists) became available, and even lucrative, leading to dramatic increases in use across all stages of the disease (Figure 2).[9-11] This phenomenon essentially lowered the threshold for treatment with ADT injections due to ease of use, patient acceptability as they no longer needed their testicles removed, biological plausibility, and low appreciation for side effects of chemical castration among the surgical specialists prescribing ADT (i.e., urologists) with little training in primary care.

A2.2 Lucrative business practice thwarted by Medicare payment reform

The story of Medicare reimbursement for ADT is a fascinating example of how financial incentives can drive medical overuse.[9] In short, Medicare reimbursed providers at 95% of the average wholesale price for these injections throughout the 1990s making it profitable since many providers acquired the drug at 82% or less of the average wholesale price.[12] Up to 40% of urology practice revenues were derived from this business practice in some cases.[13] Orchiectomy was driven out of practice, and thresholds for castration were lowered such that nearly half of prostate cancer patients received ADT by 2000.[10] Despite a stable evidence-base, more patients were getting injections in cases where there was no evidence to support use (e.g., primary treatment) alongside a growing awareness of harms. When the Medicare Part B tab for ADT injections reached $1 billion in 2003, the practice came under intense scrutiny.[14] As a result, the Medicare Modernization Act reduced payments by approximately 50% leading to significant reductions in inappropriate use as published in the *New England Journal of Medicine*

by Co-Investigator Dr. Shahinian.[9,15] Despite a decrease in what was termed 'inappropriate use' of ADT for localized prostate cancer through this policy intervention, such use persists today indicating other interventions are needed.

A2.3 Growing recognition of castration harms has led to patient safety concerns
Not surprisingly, the side effects of castration are common and impact a host of physiologic mechanisms that rely on the male hormone testosterone.[16] Castration results not only phenotypic changes due to feminization, but also osteoporosis, metabolic syndrome, cardiovascular disease, loss of sexual function, and decrements to overall quality of life (Table 1).[17] Evidence also suggests the risks of diabetes,[18] cataracts,[19] deep vein thrombosis,[20,21] stroke[22] and even acute cardiac death[23] all increase for men receiving ADT. This led the American Cancer Society and American Heart Association to issue a 2010 consensus statement on the importance of secondary preventative measures for men treated with ADT.[24]

A2.4 Reasons castration harms overlooked by providers and patients
ADT decreases the serum PSA level, a biomarker of prostate cancer activity, falsely reassuring people there is a 'remission' of the prostate cancer. This is potentially harmful in at least 2 ways. First, depriving prostate cancer cells of testosterone too early in the disease process may foster castration resistance, limiting effects when it is actually needed (e.g., metastatic setting).[25,26] Second, PSA is a poor surrogate marker for survival in localized disease. That is, lowering PSA in localized disease is not associated with improved overall survival, creating false optimism.[6,27] In addition, surgical specialists are prescribing a drug with devastating metabolic and cardiovascular effects creating a disconnect between treating PSA levels and the consequences, often dealt with in primary care. While lowering PSA might make sense on the surface, understanding beliefs and preferences for using ADT is a critical step in stopping its low value use. In many respects, this is an ideal model for understanding de-implementation of low value cancer care.

A3. Provider barriers for de-implementation of low value castration are critical, yet unknown
The majority of ADT is prescribed by urologists across all stages of prostate cancer.[28] Therefore, this proposal will focus on urologists and their patients. Our preliminary data (Section **B1**) indicate thousands of men are at risk of ongoing low value castration, especially when it comes to castration for localized disease, with tremendous variation across integrated delivery system facilities. Indeed, this calls for effective deimplementation strategies grounded in an understanding of context, provider preferences, and evidencebased behavior change techniques.[29-31] *Moreover, a significant scientific and clinical knowledge gap remains in prioritizing which barriers to stopping castration in low value settings need to be targeted for effective de-implementation*. While a major focus in this study pertains to barriers, and prioritizing and overcoming barriers, facilitators for stopping ADT that are transferable across settings also need to be considered. In addition, using a discrete choice experiment (Section **C2.1**), we will be able to prioritize both positive (facilitators, preferences) and negative factors (barriers) to guide theory-based de-implementation strategies as a promising stakeholder-based approach applicable to other low value cancer care.

A4. The benefits of unlearning ineffective, low-value clinical practices and ties to behavior change
Unlearning routinized clinical practices is challenging even if they are no longer or never were considered effective.[32,33] This is particularly true when it comes to treating patients with cancer

where provider reluctance to hold off on treatment is often a significant barrier to stopping or not initiating treatment when there are no symptoms. Unlearning clinical behaviors such as prescribing ADT in low evidence settings can have substantial benefits. First, patients are no longer subjected to treatment harms with little to no benefit. Second, unlearning misaligned castration practices can provide opportunity for more efficient, higher value use of specialists. Last, acquiring the skill of unlearning can increase flexibility and willingness to adapt to evidence more proactively.[33] We believe unlearning is captured in the Behavioral Regulation domain of the Theoretical Domains Framework (TDF), our behavior change framework, for which there are evidencebased behavior change techniques to consider. This novel TDF connection to a limited unlearning literature may play a significant role in advancing de-implementation science.

A5. Strategies to stop chemical castration as prostate cancer treatment are sorely needed

De-implementation, or stopping practices that are not evidence-based, has tremendous potential to improve patient outcomes and mitigate rising healthcare costs.[29,30] This is important given recent campaign attempts to curb overuse of services. In fact, one group has called for including castration as primary prostate cancer treatment in the next generation of *Choosing Wisely*.[34] De-implementation efforts have addressed analgesic[35] and antibiotic[36] use, glucose control,[37] and blood transfusions.[38] For this study, stopping low value castration might help prevent fractures, heart disease, and metabolic syndrome, preserve sexual function, in addition to freeing up provider time and decreasing pharmacy spending.

2 OBJECTIVES

Specific Aim 1: To assess preferences and barriers for de-implementation of chemical castration in prostate cancer. The goal of Aim 1 is to clarify barriers and facilitators to stopping castration with ADT as primary prostate cancer treatment using an individual behavior change framework, the Theoretical Domains Framework (TDF).[70] This approach will identify key barriers to de-implementation of low value ADT-based castration. We will conduct semi-structured interviews with urologists to clarify preferences for (i.e., facilitators) and barriers to stopping ADT use. This will prepare us for development of a theory-based discrete choice experiment (DCE) among a national sample of urologists in Aim 2 to quantify the relative importance of barriers, and to direct intervention strategy tailoring to increase acceptability and effectiveness. Using TDF is state-of-the-art, and embedding it within a DCE is extraordinarily innovative.

Specific Aim 2: To use a discrete choice experiment, a novel barrier prioritization approach, for deimplementation strategy tailoring. The goal of Aim 2 is to then prioritize barriers and facilitators to deimplementation of chemical castration with ADT discovered in Aim 1. The highest priority barriers will need to be addressed during strategy development and tailoring for our pilot interventions in Aim 3 to support acceptability and feasibility in practice. We will accomplish this using a discrete choice experiment (DCE), a method in which respondents (urologists) react to hypothetical choice sets based on a combination of attributes (characteristics of the product under study, in this case the approach to de-implementing ADT) and levels (descriptors of each attribute). In our DCE, the barriers and themes with the highest frequency

and most conflicting beliefs across respondents identified in Aim 1 will be refined and presented as the “attributes” and associated levels will be developed. In short, we will use data obtained from Aim 1 to develop TDF-based choice sets for inclusion in a national urologist discrete choice experiment. Once we have the most important, not just most common or conflicting, themes and barriers based on a national urologist DCE, we can select the most effective evidence-based behavior change techniques to direct deimplementation tailoring efforts in Aim 3.[39-41,46,47,77] Marketing expert Dr. Sriram (Co-I) will align our efforts with state-of-the-art discrete choice and marketing practices.

Specific Aim 3: To pilot two tailored de-implementation strategies to reduce castration as localized prostate cancer treatment. Based on findings from Aims 1 and 2, Aim 3 pilot work plays a critical role to help us understand the acceptability, feasibility, and scalability of these complex interventions in preparation for a full-scale randomized de-implementation evaluation trial.[45] In fact, the UK Medical Research Council guidance indicates piloting is essential to complex intervention development and testing prior to large-scale evaluation.[93] The main goal of both pilot interventions will be to decrease castration rates for patients with localized prostate cancer, but to do this in a way that is acceptable to the clinicians who treat these patients. We are purposely choosing intervention strategies from opposite ends of the behavior change continuum because of their evidence-based potential to change provider behavior. Specifically, we are selecting one approach (formulary restriction policy) that operates at the organizational level and is widely perceived as a forcing function, giving providers little leeway to exercise judgment. The other, physician/patient shared decision-making, operates at an individual and dyadic level, and is perceived as maximizing the opportunity for discussions between patients and providers. The first approach requires little to no learning on the part of providers, while the second requires considerable upfront learning (“cost” to the provider and possibly also to the patient). This approach sets up a testable hypothesis for our subsequent comparative effectiveness trial, that a blunt de-implementation policy may be effective in the short term but that it will lose its effects as providers learn work-arounds. Conversely, a shared or informed decision-making approach to de-implementation might take longer to observe measurable decreases in castration rates, but its effects will create sustainable change as providers internalize and routinize this clinical practice.[94]

Specific Aim 4: To conduct a secondary data analysis using national VA CDW, workforce (VSSC), and Central Cancer Registry data, exploring facility factors associated with use of low value ADT. This information could potentially inform development of Aims 2 and 3 of our study.

3 EXPECTED RISKS/BENEFITS

Aim 1: no UM patients or providers will be interviewed for Aim 1. Only risk is to VA patients and providers.

Aims 2 and 3: these aims have not yet been developed and sites are not yet selected.

Aim 4: Only VA data will be used. Only risk is to VA data.

4 ELIGIBILITY

VA urologists (and possibly other providers prescribing a significant amount of ADT) from VA facilities with the highest and lowest use of castration as primary treatment who express interest in prostate cancer (PC) care will be eligible to participate in an interview. VA patients from high outlier sites identified as receiving ADT as primary prostate cancer treatment will be eligible to participate in an interview. These criteria are necessary in order to maximize the likelihood that data collected from participants will address our study aims.

VA patients with dementia or other significant mental impairment noted in their medical record will be excluded from participation. There will be no benefit to patients from participation in this study.

We will not exclude patients enrolled in another protocol.

5 SUBJECT ENROLLMENT

No subject enrollment will take place at UM.

VA PROVIDERS:
We will purposefully sample up to 20 urologists from high outlier facilities with highest and lowest use of chemical castration with androgen deprivation therapy (ADT) as primary treatment. Facilities will be updated using our algorithm combined with Medicare claims data for years 2016 and 2017 obtained from the VA Information Resource Center (VIReC) to validate we are not missing unidentified prostate cancer treatment outside VA.

Provider data from facilities with the highest and lowest rates of chemical castration for localized disease will be collected using lists of providers from the most recent Federal Practitioner directory and national urologist email listserv. We will identify Urology Chiefs at each site using lists of providers from the most recent Federal Practitioner directory and national urologist email listserv. Dr. Skolarus will email Urology Chiefs, describe participation in the study, and request approval to contact facility urologists for interviews.

Urologists will be emailed a study information sheet (to be submitted with a future amendment prior to start of recruitment activities) briefly describing the nature and purpose of the study as well as the types of questions they will be asked. The option to refuse participation will be clearly stated. Urologists who respond to emails agreeing to participate will be contacted either by phone or email and screened for purposeful sampling (e.g., do they routinely prescribe ADT). Any urologist who has experience caring for prostate cancer patients on ADT and expresses interest in prostate cancer care will be eligible to participate. Providers who are eligible and agree to be interviewed will be contacted by phone or email and scheduled for an interview. If email responses are below our target recruitment number, we may follow up recruitment emails to providers with 1 or 2 phone calls. We will also consider interviewing non-physician providers (e.g., nurse practitioners) if they prescribe a significant amount of ADT.

VA PATIENTS:
We will use VA cancer registry data for years 2016 and 2017 to identify patients at high outlier sites on primary ADT for prostate cancer. Patients will be ineligible if they have dementia or other significant mental impairment noted in their medical record. Patients will be mailed a recruitment letter and study information sheet (to be submitted with a future amendment prior to start of recruitment activities)

describing the nature and purpose of the study as well as the types of questions they will be asked. The option to refuse participation will be clearly stated. Patients that do not opt out will be contacted by phone a week later and invited to participate. We will attempt up to 5 or 6 attempts per patient, including leaving voice mails and providing call-back information. Patients will be scheduled for a phone interview at a date and time of their choosing. We plan to conduct up to 15 patient interviews from high outlier sites.

6 STUDY DESIGN AND PROCEDURES

AIM 1:

All interviews conducted for Aim 1 will involve VA providers and patients only. UM investigators will help develop and refine the provider and patient interview guides. Drs. Wittman and Skolarus may assist VA staff with provider and patient interviews. VA staff conducting interviews have many years' experience conducting qualitative data collection. We have been granted waivers of written informed consent and HIPAA authorization by the AAVA IRB.

We will interview urologists (and possibly other providers) and patients from facilities with the highest and lowest castration rates using androgen deprivation therapy (ADT) across VHA. We will start by sending emails to VA Urology Chiefs (UCs) and VA Medical Center Directors (MCDs) at high outlier sites. At sites that have no Urology Chief on staff, we will obtain approval as requested by the MCD from others in VA leadership such as COS, DCOS, Specialty Chiefs, Section Chiefs, as well as Research staff when requested. These situations will be dealt with on a case-by-case basis. We will attempt to contact providers up to 5 times via email, phone, or VA instant messaging. We will confirm provider eligibility prior to scheduling an interview. (Please see attached provider recruitment email and follow-up eligibility email). We will attempt to interview up to 2 providers at each site. If provider response from some sites is insufficient, we will increase the number of providers interviewed at each site to up to 4 and/or send emails to the UCs and MCDs at additional high outlier facilities. We will continue in this manner until all 20 provider interviews are complete or until we feel we have reached saturation, whichever comes first. We will consider interviewing non-physician providers if they prescribe a significant amount of ADT.

Similarly, we will send recruitment letters and study information sheets to patients at high outlier facilities. We will attempt up to 5 or 6 attempts per patient, including leaving voice mails and providing call-back information. We will attempt to interview 1-2 patients from each site, with no more than 15 interviews total. If patient response from some sites is insufficient, we will increase the number of patients interviewed at each site to up to 4 and/or send recruitment letters and study information sheets to patients at additional high outlier sites. We will continue in this manner until all 15 patient interviews are complete or until we feel we have reached saturation, whichever comes first. Patients will be mailed a $20 gift card following their completion of the interview.

We will pilot provider interviews with study consultants. Pilot interviews will be conducted by phone and in person and will NOT be audiotaped. We will also obtain feedback on the patient interview guide from CCMR's Veteran Research Engagement Council (VREC). We will refine the draft semi-structured interview guides for providers and patients to elicit beliefs and attitudes regarding starting and stopping ADT as localized prostate cancer treatment, as well as informed decision-making preferences, and to ensure it can be completed in a timely fashion. Interview guides are developed iteratively - questions are developed, tested, and then refined based on what one learns from asking participants these questions. However, any substantial change or addition to interview guide questions will be submitted to the IRB for approval.

Semi-structured interviews with both patients and providers will be recorded using the Olympus DS-7000 DVR so that authorized study staff can turn the interview responses to written text to help identify common themes. Each phone interview will last approximately 30 - 45 minutes. Please note that we will ask permission to record interviews. After each interview, the audio file of the recording will be uploaded to a restricted folder located on a secure VA computer server protected behind the VA firewall. Only authorized study staff will have access to this folder. Once the interview information is located on the VA server, the original interview recording will be deleted from the recording device according to VA policy.

Interview data will be transcribed, coded and entered into NVivo software for analysis. We will use a preliminary coding scheme based on the Theoretical Domains Framework (TDF) and prior work by Huijg and Birken consisting of a three step process including: 1) coding affirmative and negative utterances regarding ADT use as localized treatment into TDF domains, 2) collecting responses across respondents into themes, 3) tallying the total number of mentions per theme, as well as conflicting beliefs within a theme (e.g., ADT is good vs. ADT is bad), according to the TDF domains, with particular emphasis on those included in our conceptual model. This qualitative work will inform Aim 2 and gather rich information for our proposed pilot intervention strategies.

We will provide a summary of results to participating providers and patients upon request once results are available. These summaries will contain only aggregate data and/or broad summaries and will be submitted to the IRB for approval prior to dissemination.

All research data will be de-identified at the termination of the study, if not sooner. Study data will be moved to the VA CCMR data repository and destroyed by the CCMR data manager six (6) years following the end of the Fiscal Year after completion of the research project as described in the VA Records Control Schedule.

AIM 2:
The goal of Aim 2 is to then prioritize barriers and facilitators to de- implementation of chemical castration with ADT discovered in Aim 1. The highest priority barriers will need to be addressed during strategy development and tailoring for our pilot interventions in Aim 3 to support acceptability and feasibility in practice. We will accomplish this using a discrete choice experiment (DCE), a method in which respondents (urologists) react to hypothetical choice sets based on a combination of attributes (characteristics of the product under study, in this case the approach to de-implementing ADT) and levels (descriptors of each attribute). In our DCE, the barriers and themes with the highest frequency and most conflicting beliefs across respondents identified in Aim 1 will be refined and presented as the "attributes" and associated levels will be developed. In short, we will use data obtained from Aim 1 to develop TDF-based choice sets for inclusion in a national urologist discrete choice experiment. Once we have the most important, not just most common or conflicting, themes and barriers based on a national urologist DCE, we can select the most effective evidence-based behavior change techniques to direct de-implementation tailoring efforts in Aim 3. Marketing expert Dr. Sriram (Co-I) will align our efforts with state-of-the-art discrete choice and marketing practices.

AIM 3:

Please note, the Aim 3 pilot and subsequent comparative effectiveness trial will be conducted at the VA Ann Arbor Healthcare System. Based on findings from Aims 1 and 2, Aim 3 pilot work plays a critical role to help us understand the acceptability, feasibility, and scalability of these complex interventions in preparation for a full-scale randomized de-implementation evaluation trial. In fact, the UK Medical Research Council guidance indicates piloting is essential to complex intervention development and testing prior to large-scale evaluation. The main goal of both pilot interventions will be to decrease castration rates for patients with localized prostate cancer, but to do this in a way that is acceptable to the clinicians who treat these patients. We are purposely choosing intervention strategies from opposite ends of the behavior change continuum because of their evidence-based potential to change provider behavior. Specifically, we are selecting one approach (formulary restriction policy) that operates at the organizational level and is widely perceived as a forcing function, giving providers little leeway to exercise judgment. The other, physician/patient shared decision-making, operates at an individual and dyadic level, and is perceived as maximizing the opportunity for discussions between patients and providers. The first approach requires little to no learning on the part of providers, while the second requires considerable upfront learning ("cost" to the provider and possibly also to the patient). This approach sets up a testable hypothesis for our subsequent comparative effectiveness trial, that a blunt de-implementation policy may be effective in the short term but that it will lose its effects as providers learn work-arounds. Conversely, a shared or informed decision-making approach to de-implementation might take longer to observe measurable decreases in castration rates, but its effects will create sustainable change as providers internalize and routinize this clinical practice.

AIM 4:
In Aim 4 (as an extension of our goals for Aim 1), we will explore facility level factors associated with low

value ADT use in clinically localized prostate cancer. We plan to retrospectively analyze data from VA facilities across the United States to determine what facility level factors are associated with low value ADT use in clinically localized prostate cancer. We hypothesize that academic affiliation will be associated with higher value prostate cancer care. More broadly, this work can begin to fill knowledge gaps regarding academic affiliations and the value of specialty care delivery in VA.

Using national VA CDW, workforce (VSSC), and Central Cancer Registry data, we will analyze rates of ADT use in localized prostate cancer for VA facilities from 2016-2017. We will separate facilities into quartiles of low value ADT use and use regression models to identify those factors associated with higher value prostate cancer care (e.g., urologist workforce, resident number, hospital size, medical school affiliation, region). We will also examine the extent to which changes in low value ADT use over time are associated with changes in facility level characteristics. To better understand the influence of facility level factors on low value specialty care, we will identify facilities that changed quartiles of low value ADT use over the study period. We will then identify changes in facility factors associated with corresponding changes in low value ADT use using regression models. For example, if loss of urologist workforce was associated with increasing low value care this may inform strategies to proactively engage facilities facing specialty care recruitment challenges. This information could potentially inform development of Aims 2 and 3 of our study.

7 DATA COLLECTION AND MANAGEMENT PROCEDURES

AIM 1: Only data from VA databases will be collected for participant identification and screening purposes. This data will be collected by the VA study data manager.

PROVIDERS:
For the semi-structured provider interviews, we will sample up to 20 VHA urologists from VHA facilities with the highest and lowest use of castration as primary treatment. We will use preliminary data from Dr. Skolarus' CDA but then update the data using CDW Oncology data for the years 2016 and 2017 once our DART application is approved. We are also applying for access to Medicare claims data from VA Information Resource Center (VIReC) to validate we are not missing unidentified treatment with surgery or radiation therapy outside VHA. We plan to pull Medicare data on
up to 20,000 patients. We will identify Urology Chiefs at each site using lists of providers from the most recent Federal Practitioner directory and national urologist email listserv. If possible, we will use CDW data to identify providers who meet the criteria of having experience caring for patients on ADT.

PATIENTS
We will use VA cancer registry data for years 2016 and 2017 to identify patients at high outlier sites on primary ADT for prostate cancer. Patients will be ineligible if they have dementia or other significant mental impairment noted in their medical record.

ACCESS TO DATA:
All identifiers, including interview recordings, will be stored in access restricted folders on VA servers behind the VA firewall. Only key study team members added to the AAVA IRB approved protocol personnel list will have access to data files containing PHI/PII. All personal identifiers will be stripped from the written verbatim transcripts of the interviews. Subjects will be instructed at the start of the interview to refrain from mentioning names of colleagues or from identifying the medical center.

DATA SAFETY MONITORING PLAN (DSMP):

Dr. Skolarus will be responsible for reporting all adverse events that might arise during the course of the study to the University of Michigan and the Ann Arbor Veterans Affairs Health System IRB. Adverse Events during this study would likely consist only of breaches in confidentiality. The following precautions have been taken to prevent this. However, should such breaches occur, Dr. Skolarus will report these occurrences to the overseeing IRBs within 48 hours.

All identifiers, including interview recordings, will be stored in access restricted folders on VA servers

behind the VA firewall. Only key study team members added to the AAVA IRB approved protocol personnel list will have access to data files containing PHI/PII. All personal identifiers will be stripped from the written verbatim transcripts of the interviews. Subjects will be instructed at the start of the interview to refrain from mentioning names of colleagues or from identifying the medical center. All research data will be de-identified at the termination of the study, if not sooner. Study data will be moved to the VA CCMR data repository and destroyed by the CCMR data manager six (6) years following the end of the Fiscal Year after completion of the research project as described in the VA Records Control Schedule.

AIMS 2: The survey/DCE will be pilot tested at study consultants' sites and refined based on feedback and any necessary troubleshooting. Once the survey/DCE is finalized, it will be disseminated to providers on the Society of Government Service Urologists (SGSU) listserv. Study staff will send email invites to up to 500 providers. The email invite will include an attached study information sheet and a link to the survey/DCE. Email invites will be sent from Dr. Skolarus' VA email account. We will send up to 3 email invites to the listserv (allowing at least one-two weeks between each invite) and collect up to 400 completed surveys/DCEs. The survey/DCE will be hosted on the Sawtooth Software platform and **all data will be collected anonymously**. Providers completing surveys/DCEs will receive a $50 Amazon eGift Card.

AIM 3: The pilot will be conducted at 4 VA sites under the oversight of the VA Ann Arbor RDC/IRB.

AIM 4:
We plan to retrospectively analyze data from VA facilities across the United States to determine what facility level factors are associated with low value ADT use in clinically localized prostate cancer. Data will be collected from national VA CDW, workforce (VSSC), and Central Cancer Registry data by the study data manager. All identifiers will be stored in access restricted folders on VA servers behind the VA firewall. Only key study team members added to the AAVA IRB approved protocol personnel list will have access to data files containing PHI/PII. Study data will be moved to the VA CCMR data repository and destroyed by the CCMR data manager six (6) years following the end of the Fiscal Year after completion of the research project as described in the VA Records Control Schedule.

8 DATA ANALYSIS

AIM 1:

Interview data will be transcribed, coded and entered into NVivo software for analysis. We will use a preliminary coding scheme based on the Theoretical Domains Framework (TDF) and prior work by Huijg and Birken consisting of a three step process including: 1) coding affirmative and negative utterances regarding ADT use as localized treatment into TDF domains, 2) collecting responses across respondents into themes, 3) tallying the total number of mentions per theme, as well as conflicting beliefs within a theme (e.g., ADT is good vs. ADT is bad), according to the TDF domains, with particular emphasis on those included in our conceptual model. This qualitative work will inform Aim 2 and gather rich information for our proposed pilot intervention strategies.

AIMS 2:

Discrete choice experiments are based on Random Utility Theory which assumes participants will select responses with the most personal utility.80,83 Because respondents respond to a variety of choice sets, we will be able to estimate the relative priority of our barrier attributes and their levels. We will model urologists stated preferences providing quantitative information about the relative value, or utility, providers place on barrier attributes such as *physician autonomy* or *clinical time*, for example, using the equations below. There are ~250 urologists on the listserv. If 50% respond: 125 surveys with ~5 scenarios – 625 scenarios x 5 attributes = 3125 data elements for analysis. Dr. Wiitala is an expert in multi-level and multinomial regression techniques and will conduct the analyses with direction from Drs. Hawley and Sriram given their DCE expertise. Our methods will adjust for dependency of responses within individuals as they respond to different choice sets and will be modeled after published DCEs according to the following example equation:

Utility = (Constant) +β1 (e.g., physician autonomy) + β2 (e.g., clinical time) …
We will assess for model fit and need for random parameters among the attributes. Attribute levels will range from -1 for our reference level to +1 for the alternative to allow determination of relative importance.80 Our outcomes will be based on the beta parameter values (*β1, β2, etc.)* and standard errors that correspond to each attribute where a negative value will indicate preference for the reference group, statistical significance will be set at 0.05. Once we have our leading barrier attributes and corresponding TDF domains, we will select the most relevant candidate evidence-based behavior change technique components based on prior work by Michie et al.47 to guide tailoring of pilot de-implementation interventions. We also plan to adjust our models for facility-level ADT rates, and perform a subgroup analysis for facilities with high primary ADT rates to better understand barriers to tailor towards

9 QUALITY CONTROL AND QUALITY ASSURANCE

AIM 1:

Interviews will be audiotaped and transcribed verbatim for content. We will conduct analyses concurrently with ongoing interviews, if timing permits, to inform subsequent data collection and analysis. We will use a preliminary coding scheme based on the TDF and prior work by Huijg et al.,41 and Birken et al.,76 consisting of a three step process including: 1) coding affirmative and negative utterances regarding ADT use as localized treatment into TDF domains, 2) collecting responses across respondents into themes (e.g., "ADT prevents cancer spread" into a 'ADT is beneficial' theme, "urologists should be able to treat patients as they wish" into a 'Physician autonomy' theme), 3) tallying the total number of mentions per theme, as well as conflicting beliefs within a theme (e.g., ADT is good vs. ADT is bad), according to the TDF domains, with particular emphasis on those included in our conceptual model. Study interviewers and qualitative analysts will both independently review and code transcripts and meet regularly to compare coding results until reaching agreement on code definitions and establish the reliability of the coding process (>80% simple agreement). During this process, study investigators and interviewers will also meet to categorize the codes into TDF domains, identify emerging themes, and document ongoing data interpretation in memos. Once data are coded, we will use QSR NVivo software to organize the data. Drs. Skolarus and the research team will meet regularly to discuss code summaries and memos, developing findings with a focus on informing the Aim 2 discrete choice tool. At the end of this aim we will have identified the highest frequency themes and themes with conflicting provider and patient beliefs across TDF domains for de-implementing ADT.

AIMS 2 AND 3: tbd

10 STATISTICAL CONSIDERATIONS

Please see above for information on qualitative analysis.

PILOT OUTCOMES

Primary Outcome Measures

A. Feasibility – Site level

- Title: Percentage of approached pilot sites with Medical Center Director approval to implement the intervention (Order Check (OR) or Progress Note/Patient Handout (SC))
    - Description: The percentage of pilot sites asked to participate that received MCD approval to implement the intervention (Order Check or Progress Note/Patient Handout)
    - Time frame: Within 1 month.

- Title: Percentage of director-approved pilot sites with intervention implementation.

- Description: The percentage of approved pilot sites with fully operationalized intervention within the site. Depending on randomization arm, this includes either health factor placement or script assignment prior to at least one patient visit.
- Time frame: Within 3 months of approval.

B. Feasibility – Clinic level

- Title: Percentage of total pilot site clinics with intervention implementation.
- Description: The percentage of clinics at approved pilot sites with at least 1 health factor assigned and/or at least 1 progress note assigned to a provider. Clinics may include Urology, Medical Oncology, and Radiation Oncology.
- Time frame: Within 3 months of intervention implementation.

Secondary Outcome Measures

A. Reach

- Title: 1.00 - The percentage of providers prescribing ADT for prostate cancer sent an information sheet who did not opt out of the study.
- Description: The percentage of providers in the study prescribing ADT for prostate cancer sent an information sheet who remained in the study.
- Time frame: Within 6 months of intervention.

B. Penetration

- Title: Percentage of SC intervention clinic notes assigned to providers that were signed.
- Definition: Percentage of clinic notes assigned to ADT providers by the study team that were successfully used by providers (signed and became part of EMR).
- Time frame: Within 6 months of intervention.

- Title: Percentage of OR intervention order checks justified.
- Definition: The number of low-value ADT orders with justification / the total number of low-value ADT orders placed.
- Time frame: Within 6 months of intervention.

11 REGULATORY REQUIREMENTS

11.1 Informed Consent

- *The AAVA IRB has granted waivers of written informed consent and HIPAA authorization for Aim 1 of this study.*
- *VA providers and patients will be sent a study Information Sheet and verbal consent will be obtained by study staff and interviewers during recruitment calls and at the start of the interview.*

11.2 SUBJECT CONFIDENTIALITY

- *Confidentiality will be protected by restricting access to identifiable research data to key authorized study personnel only. In particular, data*

will be stored on VA servers and in study folders that can only be accessed by specified study personnel. We will maintain an electronic list of potential participants so we can invite them to participate. The digital recordings will be stored in electronic files with filenames that indicate only generic roles and facility ID. A written verbatim transcript will be created for each participant, but all personal identifiers will be stripped from the transcript. Subjects will be instructed at the start of the interview to refrain from mentioning names of colleagues or from identifying the medical center. The transcripts and digital recordings will be stored in access-limited files in a project specific folder maintained on a VA server behind the VA firewall. All study data will be accessible only by approved study staff.

- *Data for the Aim 2 DCE survey is collected anonymously.*
- *The following UM study team members are also listed on the VA IRB and will have access to identifiers: Ted Skolarus, Sarah Hawley, Daniela Wittmann, Tabitha Metreger.*
- *Access to personally identifiable information is required for recruitment purposes, to confirm diagnoses and eligibility and to verify contact information. Access to protected health information is required to fulfill the Aims of this study.*
- *A Certificate of Confidentiality is not required for this study.*

11.3 Unanticipated Problems[1]

- Dr. Skolarus will be responsible for reporting all adverse events that might arise during the course of the study to the University of Michigan and the Ann Arbor Veterans Affairs Health System IRB. Adverse Events during this study would likely consist only of breaches in confidentiality. As outlined above, precautions have been taken to prevent this. However,

[1] The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to subjects or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research (in the guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

An incident, experience, or outcome that meets the three criteria above generally will warrant consideration of substantive changes in order to protect the safety, welfare, or rights of subjects or others.

should such breaches occur, Dr. Skolarus will report to the UM IRB according to the standard reporting schedule listed here: https://az.research.umich.edu/medschool/guidance/adverse-event-reporting.

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APPENDICES

Email to Urology Chief

Email to MCDs

Provider Information Sheet

Provider Recruitment and Eligibility Email

Provider Interview Guide_providers who do NOT use LV-ADT

Provider Interview Guide_providers who use LV-ADT

List of VHA facilities

Please note: the following recruitment materials will be submitted with a future project modification. Patient recruitment activities will not begin until IRB approval has been obtained for these materials:

Patient Recruitment Letter

Patient Information Sheet

Patient Recruitment Phone Script

Patient Interview Guide