

Examples of Funded Grants in Implementation Science

Overview

The National Cancer Institute (NCI) frequently receives requests for examples of funded grant applications. Several investigators and their organizations agreed to let Implementation Science (IS) post excerpts of their dissemination and implementation (D&I) grant applications online.

About

We are grateful to the investigators and their institutions for allowing us to provide this important resource to the community. To maintain confidentiality, we have redacted some information from these documents (e.g., budgets, social security numbers, home addresses, introduction to revised application), where applicable. In addition, we only include a copy of SF 424 R&R Face Page, Project Summary/Abstract (Description), Project Narrative, Specific Aims, and Research Strategy; we do not include other SF 424 (R&R) forms or requisite information found in the full grant application (e.g., performance sites, key personnel, biographical sketches).

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424 R&R and PHS-398 Specific

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SF 424 R&R Face Page

PI: Skolarus, Ted Albert

Grant Number: 1 R37 CA222885-01

Title: De-implementation of low value castration for men with prostate cancer

FOA: PAR16-238

FOA Title: DISSEMINATION AND IMPLEMENTATION RESEARCH IN HEALTH (R01)

Organization: University Of Michigan at Ann Arbor

Department: Urology

Senior/Key Personnel: Ted Skolarus

Organization: Regents of the University of Michigan

Role Category: PD/PI

Project Summary

Project Background: Prostate cancer is the leading male cancer. One in three men with prostate cancer is chemically castrated at some point with long-acting injectable drugs (i.e., androgen deprivation therapy or ADT). This impacts the well-being of thousands of men annually. Although some patients benefit in terms of survival and symptom improvement, chemical castration with ADT is also commonly performed when there are little to no health benefits to patients raising questions of low value care. A growing awareness of castration harms (e.g., heart attack, osteoporosis, loss of sexual function) creates patient safety concerns. Despite this, ADT use in low value cases, such as for localized prostate cancer treatment, persists. Ineffective and harmful practices such as chemical castration of prostate cancer patients with ADT outside of the evidence base are ideal targets for de-implementation. De-implementation, or stopping low value practices, has the potential to improve patient outcomes and decrease healthcare costs. However, provider preferences regarding de-implementation are not well understood, and possible de-implementation interventions range from blunt formulary restriction policies to shared decision-making. Both intervention strategies need tailoring based on provider input for acceptability and feasibility in clinical practice, including piloting prior to trialing. As many medical practices lack evidence and cause harm, robust, behavioral theory-based methods for incorporating provider preferences into de-implementation strategy development will advance both implementation research and practice.

Project Objectives: This study will use a theory-based, mixed methods approach to identify, tailor and pilot two different de-implementation strategies that vary widely in delivery, impact, and expected results for reducing low value ADT use, in preparation for a randomized comparative effectiveness trial.

Project Methods: This innovative mixed-methods research program has three aims. Aim 1: To assess preferences and barriers for de-implementation of chemical castration in prostate cancer. Guided by the Theoretical Domains Framework, urologists from facilities with the highest castration rates across an integrated delivery system will be interviewed to identify key preferences and de-implementation barriers for reducing castration as prostate cancer treatment. This qualitative work will inform Aim 2 while gathering rich information for two proposed pilot intervention strategies. Aim 2: To use a discrete choice experiment, a novel barrier prioritization approach, for de-implementation strategy tailoring. A national survey of urologists will prioritize key barriers identified in Aim 1 for stopping castration as localized prostate cancer treatment using a discrete choice experiment design. These quantitative results will identify the most important barriers to be addressed through tailoring of two pilot de-implementation strategies in preparation for Aim 3 piloting. Aim 3: To pilot two tailored de-implementation strategies to reduce castration as localized prostate cancer treatment. Building on findings from Aims 1 and 2, two de-implementation strategies will be piloted. One strategy will focus on formulary restriction at the organizational level and the other on physician/patient decision-making. Outcomes will include acceptability, feasibility, and scalability in preparation for an effectiveness trial comparing these two widely varying de-implementation strategies. This innovative approach to de-implementation strategy development will transform how and why castration is performed for localized prostate cancer through combining provider preferences and strategy tailoring. This work will advance de-implementation science for low value cancer care and foster participation in a subsequent de-implementation evaluation trial by addressing preferences and concerns through pilot tailoring.

Project Narrative

Men with prostate cancer are often castrated with long-acting injectable drugs. Although many benefit, these drugs are also used in patients with little or nothing to gain. The best ways to stop this practice are unknown, and range from blunt pharmacy restrictions to shared decision-making. This study will refine and pilot two different de-implementation strategies for reducing use of these drugs among those unlikely to benefit in preparation for a comparative effectiveness trial. Due to an aging population of men with prostate cancer, reducing castration in those least likely to benefit promotes quality care and quality of life. This study will transform how and why low value castration is practiced, and advance the science behind stopping low value, even harmful, cancer treatments.

Specific Aims

Prostate cancer is the leading male cancer. One in three men with prostate cancer is chemically castrated at some point with long-acting injectable drugs (i.e., androgen deprivation therapy or ADT). This impacts the well-being of thousands of men annually. Although some prostate cancer patients benefit from ADT in terms of survival and symptom improvement, chemical castration is also commonly performed when there is no high level evidence for use and little to no health benefits to patients raising questions of low value care. A growing awareness of iatrogenic harms (e.g., heart attack, osteoporosis, loss of sexual function), coupled with a lack of evidence supporting chemical castration in many cases, creates patient safety concerns. Despite this, chemical castration with ADT in low value cases persists as in the case of localized prostate cancer treatment.

Ineffective and harmful practices such as chemical castration of prostate cancer patients outside of the evidence base are ideal targets for de-implementation. De-implementation, or stopping low value practices, has the potential to improve patient outcomes and decrease healthcare costs. For example, stopping chemical castration as localized prostate cancer treatment could prevent harm, limit spending, and maintain survival. However, provider and patient preferences regarding de-implementation are not well understood, and possible de-implementation interventions range from blunt policies to shared decision-making. Blunt policy interventions such as formulary restriction of ADT (e.g., pre-authorization, order templates) might seem warranted given patient safety concerns, yet could result in significant provider resistance and work-arounds if introduced poorly. More nuanced, patient-centered interventions such as shared decision-making (e.g., decision aid, values elicitation) likely involve extra clinical time. Both intervention strategies need tailoring for acceptability and feasibility in clinical practice, including piloting prior to trialing. The messaging and operation of strategies to stop low value cancer care hinges on stakeholder input. As many medical practices lack evidence and cause harm, robust, behavioral theory-based methods for incorporating provider preferences into de-implementation strategy development will advance both implementation research and practice.

For these reasons, we will examine urologist and patient perspectives on chemical castration with ADT in low value settings. Using a theory-based, mixed methods approach to tailor different de-implementation strategies, we will pilot interventions in preparation for a randomized comparative effectiveness trial of two different approaches that vary widely in delivery, impact, and expected results for reducing low value ADT use. We have 3 specific aims:

Specific Aim 1: To assess preferences and barriers for de-implementation of chemical castration in prostate cancer. Guided by the Theoretical Domains Framework, we will interview urologists and patients from facilities with the highest castration rates across an integrated delivery system to identify key preferences and de-implementation barriers, as well as facilitators, for reducing castration as prostate cancer treatment. This qualitative work will inform Aim 2 and gather rich information for our proposed pilot intervention strategies.

Specific Aim 2: To use a discrete choice experiment, a novel barrier prioritization approach, for de-implementation strategy tailoring. We will conduct a national survey of urologists to prioritize the key barriers identified in Aim 1 for not recommending castration as localized prostate cancer treatment using a discrete choice experiment. These quantitative results will identify the most important barriers to be addressed through tailoring of our two pilot de-implementation strategies in preparation for Aim 3 piloting.

Specific Aim 3: To pilot two tailored de-implementation strategies to reduce castration as localized prostate cancer treatment. Building on findings from Aims 1 and 2, we will refine two pilot de-implementation strategies. One strategy will focus on formulary restriction at the organizational level, and the other on decision-making at the physician/patient level. Outcomes will include acceptability, feasibility, and scalability in preparation for an effectiveness trial comparing these two widely varying de-implementation strategies across the integrated delivery system.

Impact: This innovative approach to de-implementation strategy development is directly aligned with state-of-the-art complex implementation intervention development and implementation science. We believe this study will transform how and why castration is performed for men with prostate cancer through combining trans-

disciplinary expertise, rigorous assessment of provider preferences, and de-implementation strategy tailoring. This work will broadly advance de-implementation science for low value cancer care, and foster participation in our de-implementation evaluation trial by addressing barriers, facilitators, and concerns through pilot tailoring.

Research Strategy

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

Figure 1. Variation in hormonal therapy use (i.e., castration) as primary treatment across VHA facilities

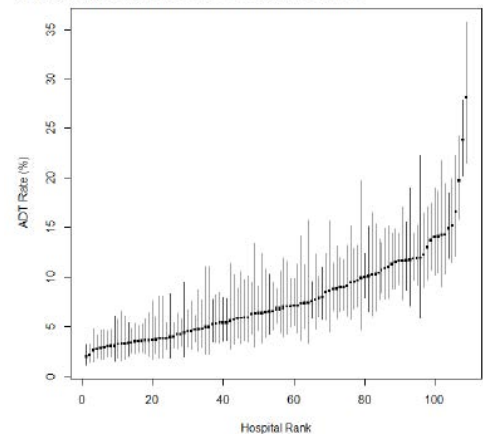
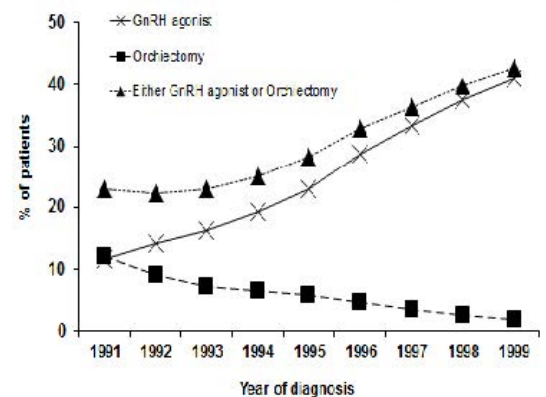


Figure 2: Increasing use of chemical castration with ADT versus surgical orchiectomy for 100,274 men with prostate cancer



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} stroke²² and even acute cardiac death²³ 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 de-implementation strategies grounded in an understanding of context, provider preferences, and evidence-based 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 evidence-based 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 analgesic³⁵ and antibiotic³⁶ 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.

A5.1 De-implementation categories and tailored de-implementation strategies

Three categories have been proposed when deciding what and how to de-implement: 1) contradicted, established, 2) unproven, and 3) novel medical practices.²⁹ Most indications for castration fall into the second category. Given the limited evidence base for castration in primary prostate cancer treatment, its cost, harms and ubiquity in other low value settings (e.g., prostate cancer recurrence), understanding how best to de-implement low value initial and ongoing castration could yield significant benefits. De-implementation strategies for unlearning castration practices will need to be tailored to provider preferences, facilitators, and barriers to maximize effectiveness.^{31,39-44} Even though we have identified two very different strategies for de-implementation (e.g., formulary restriction, shared decision-making), these are broad strategies, with considerable space in each for tailoring. In this application, we are using the term “tailoring,” often used to describe approaches to fitting implementation interventions to local context or site characteristics, to mean designing specific aspects of each strategy to increase acceptability and likelihood of effectiveness.⁴⁵ Barriers and preferences, including facilitators, for operationalization of two different de-implementation interventions represent clinically-relevant knowledge gaps this proposal will inform in preparation for a comparative effectiveness trial. We believe our quantitative discrete choice analyses will delineate the most important factors influencing ADT treatment for inclusion in our tailoring approaches.

A6. Impact: Our proposal has implications for the following cancer care stakeholders:

- **Implications for patients:** Due to the large population of prostate cancer patients, enhancing safety by promoting evidence-based use of chemical castration promotes quality care and quality of life.
- **Implications for providers:** Understanding how providers unlearn ineffective clinical behaviors is a critical step towards optimizing prostate cancer care and de-implementation of low value services.
- **Implications for low value cancer care policy:** This proposal will address important issues surrounding provider behavior change and serve as a model to decrease overtreatment more broadly. This is especially relevant given *Choosing Wisely* and a growing need for effective de-implementation.

A7. Innovation: Our focus on understanding barriers and facilitators to and priorities for de-implementation of low value services is highly innovative. Despite the call for a better understanding of how to de-implement practices shown to have more harm than benefit (including many cancer-related services such as mammography, lung cancer and PSA screening), little applied research has been conducted to inform tailoring of strategies to be most acceptable and effective for stakeholders. In addition to the topic, this proposal is innovative in that it advances cancer care and implementation science by:

- Building the evidence base for de-implementing medical interventions with unclear or no benefits. This is novel and critical given our increasing healthcare costs and the harms of overtreatment.^{29,30}
- Using a systematic, theory-based approach to tailor effective, reliable de-implementation interventions and strategies. Our use of the TDF linked to behavior change techniques is especially innovative and will enhance the tailoring of interventions significantly.^{46,47} This project will enhance our ability to map causal relationships to professional behavior change and advance implementation science.
- Better understanding acceptable ways to stop aggressive, low value cancer care. This is necessary across disease types to maximize patient welfare and control spending. Using a discrete choice experiment to prioritize barriers and guide intervention development is a novel, stakeholder-based approach applicable across low value care,⁴⁸⁻⁵⁰ and combining it with TDF is also particularly novel.

B. PRELIMINARY STUDIES

Our multi-disciplinary team is exceedingly well-positioned to successfully carry out the proposed work. We have collaborated previously. We have extensive expertise in clinical prostate cancer care, implementation research, survey & discrete choice methods, qualitative & quantitative analyses, shared decision-making, informatics tools, pharmacy applications, and theory-based intervention design and tailoring.

B1. Variation in low value castration rates indicate the need for ADT de-implementation

In preparation for this proposal, we identified current trends in ADT use as primary treatment for localized prostate cancer (Figure 1). We found persistent low value ADT and marked variation in 2014 facility level rates. While some might argue relatively low numbers of patients are unnecessarily treated, patients are routinely committed to lifelong ADT injections once the treatment decision is made. Better understanding de-implementation of ADT also opens the door to stopping more common low value use (e.g., recurrence).⁴

B2. American Cancer Society Prostate Cancer Survivorship Guidelines highlight ADT harms

As lead author of the guidelines,¹⁷ Dr. Skolarus led a team to develop clinical follow-up care guidelines for primary care clinicians. The harms of castration were stressed as they impact most long-term effect domains. In addition, Drs. Skolarus, Caram (Co-I), Shahinian (Co-I) co-authored a manuscript on ADT-associated bone disease emphasizing restriction of castration to evidence-based settings to limit unnecessary harms.⁵¹ Drs. Skolarus and Hawley (Co-I) also work closely on a randomized trial of tailored self-management strategies to address prostate cancer treatment side effects including those of ADT.

B3. De-implementation of cancer care: the case of bilateral mastectomy overuse

The growing rate of contralateral prophylactic mastectomy among women with breast cancer raises concerns about overtreatment driven by extra-scientific factors such as payment policy and media coverage akin to the ADT castration story. As highlighted by Dr. Hawley (Co-I) in peer-reviewed and media outlets,⁵² and reinforced by Montini & Graham's recent *Implementation Science* paper on de-implementation of entrenched practices,³⁰ contextualizing provider perceptions is critical to any de-implementation strategy.

B4. Extensive prior collaborations to understand prostate cancer provider behavior

Drs. Skolarus, Hollenbeck (Co-I) and Shahinian (Co-I) have characterized prostate cancer care delivery over the last decade including castration with ADT in the Medicare population.^{10,28,53-55} They found urologists prescribed 95% of ADT as initial treatment,²⁸ low bone health surveillance for ADT,⁵⁶ as well as significant provider-level variation in ADT use among patients unlikely to benefit from treatment.⁵⁷

B5. Theory-driven barrier assessment and intervention development

Dr. Sales (Co-I) has conducted several implementation research studies within and outside VA. She has developed numerous tools to guide theory-based implementation, including reminders, provider led clinics, and feedback reports.⁵⁸⁻⁶¹ She has worked with the TDF, our behavior change theory for de-implementation. This framework uses constructs from over 30 psychological behavior change theories to assess barriers and facilitators to evidence-based practice and to design interventions.³⁹ Dr. Hawley (Co-I) also has extensive experience with theory-based cancer decision-making interventions and clinical trials.⁶²⁻⁶⁵

B6. Discrete choice experiments to direct cancer care strategies

Dr. Hawley (Co-I) has extensive experience using discrete choice experiments (DCE) in chemoprevention for breast cancer, prostate and colorectal cancer screening.⁶⁵⁻⁶⁷ For example, using a DCE to learn how vulnerable North Carolina individuals value different aspects of colorectal cancer screening programs to help with strategic planning.⁶⁶ While still an emerging, novel tool in health care, DCEs are routinely used to facilitate priority setting and drive marketing strategy development in industry.^{48,49,68,69} We will use DCE to weight de-implementation barriers and guide pilot strategy tailoring (Aim 2). As such, Dr. S. Sriram (Co-I) will lend his DCE and marketing expertise to our efforts to support state-of-the-art marketing approaches.

B7. Which de-implementation factors are most important for limiting ADT-based castration? Currently, priority setting for which barriers and facilitators to address during implementation strategy development is many times a matter of convenience, gestalt and ignorance as to which are the most common barriers versus most important.^{31,40,47,61,70} The TDF was recently used to direct development of an instrument that could readily identify

hand-hygiene barriers and link them to evidence-based behavior change techniques.³¹ *While this advanced theory-based barrier assessment exists, there are no current tools to guide tailoring of (de-) implementation interventions to the most important barriers, stakeholder preferences, and facilitators as we plan to do in Aims 2 and 3.* As preliminary data for our innovative approach, we asked local urologists who treat prostate cancer to identify potential barriers to stopping castration. We identified barriers and mapped them to TDF domains and candidate evidence-based behavior change techniques (Table 1).

Table 1. Examples of barriers and TDF domains linked to evidence-based behavior change techniques for de-implementation strategy development ⁴⁷		
Barrier attribute	TDF Domain	Behavior change technique
Value of physician autonomy	Professional role \ identity	Education, modeling, persuasion
Evidence for appropriate use	Knowledge	Education
Clinical time, patient education	Environmental context / resources	Training, restriction, restructuring

Conducting qualitative work across facilities (Aim 1) and using a quantitative discrete choice technique to prioritize barriers (Aim 2) will inform tailoring of our two pilot intervention strategies (Aim 3).

B8. Informatics tools to de-implement low value prostate cancer clinical practices

Dr. Skolarus collaborates with Dr. Shelton (Consultant) and his informatics team at the Greater Los Angeles VA Medical Center. They recently developed and implemented a highly-specific computerized clinical decision support alert to remind providers, at the moment of PSA screening order entry, of current guidelines against screening elderly men for prostate cancer – essentially *de-implementation of PSA screening*. In a prospective study involving over 30,000 patients published in *Journal of General Internal Medicine*, the screening rate decreased by over 30%.⁷¹ Dr. Shelton and his team are fully supportive of development of a pilot EMR-based intervention for formulary restriction of low value ADT (See letter).

B9. Shared decision-making to inform prostate cancer treatment selection

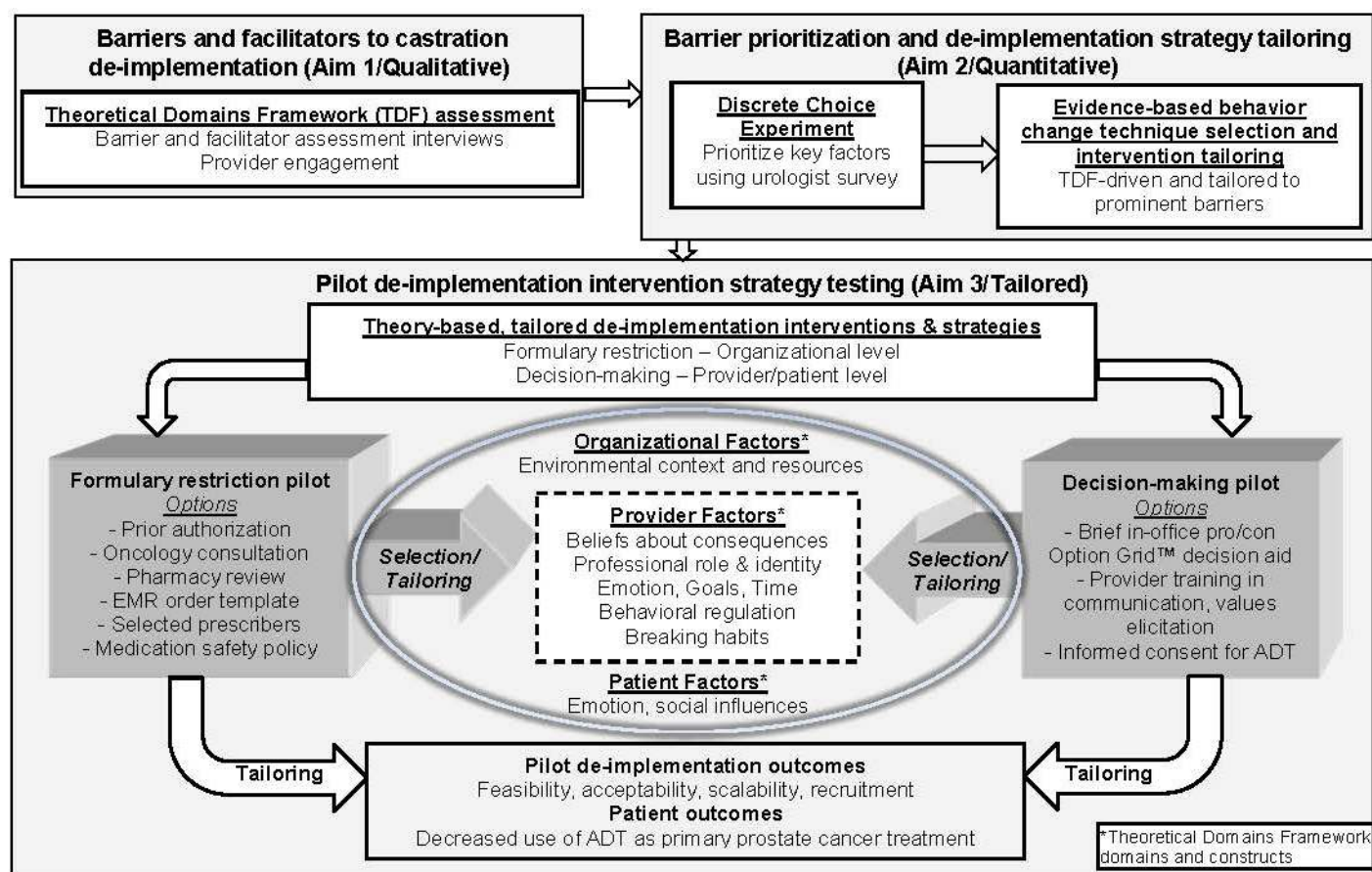
This team has tremendous clinical and research expertise in shared decision-making for cancer care. Dr. Skolarus updates an evidence- and expert opinion-based shared decision-making tool for prostate cancer decision making endorsed by the American Urological Association. In addition, Dr. Hawley (Co-I) has led decision aid studies in both breast and colorectal cancer.^{62,64} She also has experience with using Option Grid™, the potential clinical encounter decision support tool for this study.⁷² In addition, Dr. Makarov (Consultant) chaired the American Urological Association’s 2015 White Paper on ‘Implementation of Shared Decision-Making into Urological Practice,⁷³ and will support pilot intervention development (See letter).

C. APPROACH

C1. Overview and conceptual model

It is useful to consider the following conceptual model for theory-based qualitative barrier assessment (Aim 1), quantitative prioritization (Aim 2), and piloting of de-implementation strategies tailored to provider behavior change techniques (Aim 3). We highlight several TDF domains and constructs in our conceptual model that may contribute to organizational, provider, and patient behavior in the setting of ADT for localized prostate cancer. In addition, our qualitative approach allows for flexibility as we conceptualize the main issues when it comes to chemical castration. Last, the quantitative discrete choice methods (Aim 2) create significant opportunities to examine interactions among domains and constructs allowing us to select, tailor and pilot the most informed organizational and individual level de-implementation interventions in Aim 3.

Figure 3. Conceptual model for de-implementation strategy development



C1.0 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.

C1.1 Study population

Sampling, participant identification and recruitment

For the semi-structured provider interviews, we will purposefully sample 10-12 urologists from integrated delivery system facilities with the highest use of castration as primary treatment to achieve thematic saturation.^{74,75} Likewise, we will also sample 2-4 urologists from facilities with the lowest use of castration. We have already identified the facilities (Figure 1), however we will update our findings using our algorithm combined with Medicare claims data obtained from the VA Information Resource Center (VIREC) to validate we are not missing unidentified prostate cancer treatment outside VA. We will identify Urology Chiefs at each site using a national directory. Dr. Skolarus will email the Urology Chief and describe participation in the study. He and a research assistant (RA) will conduct phone interviews with up to 12 providers in high volume ADT facilities and 4 providers in low volume ADT facilities. We will screen providers through brief telephone and email surveys. Providers who consent will be asked screening questions for purposeful sampling (e.g., do they routinely prescribe ADT). Any urologist who has experience caring for more than 10 prostate cancer patients on ADT and expresses interest in prostate cancer care will be eligible to participate in semi-structured interviews. We will consider interviewing non-physician providers (e.g., nurse practitioners) if they prescribe a significant amount of ADT. To better understand patient perspectives into not initiating or stopping castration with ADT, we also plan to conduct a limited number of

patient interviews (~6) from high outlier sites. Drs. Skolarus and Hawley have used similar methods for their randomized trial.

Semi-structured provider and patient interviews

In order to maximize the likelihood that data collected from participants will address our study aims, we will pilot interviews with consultants and providers at the University of Michigan and Ann Arbor VA.⁷⁵ We anticipate the pilot process will be extremely valuable in enriching our methods prior to formal interviews. Semi-structured interviews produce rich data conveyed in the interviewee’s own words through the use of open-ended questions and tailoring of the interview to each participant, while covering relevant TDF domains. Similar to Huijg et al.,⁴¹ we will use a *target, action, context, time (TACT)* construction across TDF domains, and explore: (1) Understanding of ADT as primary prostate cancer treatment; (2) Harms of castration; (3) Behavioral determinants and barriers to delivering (receiving for patients) ADT as primary prostate cancer treatment for localized prostate cancer; and (4) Intention to treat localized prostate cancer with ADT. Using the TDF to understand provider and patient ADT behavior will help: 1) map our findings to key TDF behavioral constructs, 2) select appropriate evidence-based behavior change techniques, 3) understand barriers, facilitators and stated preferences for our de-implementation interventions, and 4) advance implementation science. Drs. Skolarus, Hawley and Sales will refine the draft semi-structured interview guide for providers and a limited number of patients (Appendix) and ensure it can be completed in a timely fashion. The interviews will last ~45 minutes with eligible providers and patients and be audiotaped.

C1.2 Aim 1 Data

Table 2. Data sources and variables for Aim 1

Information	Source	Variables
Barriers and facilitators to stopping low value chemical castration	12-16 urologists, selected patients from high ADT facilities	Semi-structured interview data coded into themes and TDF domains for use in Aim 2.

C1.3 Analysis

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. Dr. Skolarus and the RA will both independently review and code at least 2 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, see Appendix for draft codebook). During this process, Drs. Skolarus, Hawley, Sales and the RA will also meet to categorize the codes into TDF domains, identify emerging themes, and document ongoing data interpretation in memos. The RA will code the remaining transcripts. 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.⁷⁵ 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.

Specific Aim 2: To use a discrete choice experiment, a novel barrier prioritization approach, for de-implementation strategy tailoring. 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.^{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.

C2.1 Discrete choice experiment (DCE)

Rationale and tailoring of the two pilot intervention strategies

As discussed in **B6**, DCEs are techniques that facilitate priority setting outside and more recently, within health care. This stated preference method drives marketing strategy development based on stakeholder preferences for a given practice and is a promising applied approach for health care optimization.^{48,66,68,69,78} Real-world DCE examples include prioritizing provider preferences related to hospital consultant work⁷⁹ and electronic medical record use.⁸⁰ In a DCE, stakeholders, in this case urologists prescribing ADT, would need to choose between hypothetical alternatives described by themes and barrier characteristics identified from Aim 1 (i.e., attributes and levels). The 5 or 6 highest frequency and most conflicting themes based on Aim 1 findings will be varied across hypothetical examples. Through systematically varying a set of levels in a series of choice sets where providers are asked which option they most prefer, we gather critical data on castration preferences and tailoring for our pilot interventions. This results in a preference structure where certain attributes (barriers) are most important across the respondent sample. The data obtained on the levels of attributes shows which direction the attribute is most favored. In an example of whether *high* or *low physician autonomy* or *level of evidence* is driving ADT treatment decisions, for each choice set given, we will ask respondents to choose the situation that they would most prefer when prescribing ADT for their prostate cancer patients (choice A, choice B, or neither). We may ask participants: 'Please select the situation that you most prefer when prescribing ADT as primary treatment.' Candidate themes, attributes and levels include, for example, the *ability to make the final recommendation* (levels: *yes, no*), the amount of *clinical time* required (levels: *10-15 minutes, 25-30 minutes*). We will use an opt-out option to ensure realistic scenarios.^{50,80} Data from this DCE survey will identify leading themes and attributes (barriers).

Designing and fielding the national urologist DCE

As we design our DCE, it will be necessary to strike a balance between realistic clinical scenarios and design complexity to avoid respondent overload. We will decide on the number of attributes based on Aim 1 findings, likely 4-6 per scenario as suggested by the literature. The DCE will measure TDF-based themes across 10-20 choice sets, pared down using a fractional factorial approach, to a reasonable number of hypothetical scenarios per respondent to minimize respondent burden. We will use software (NGene 1.1) to construct the choice sets using a D-efficient design approach to identify the least number of choice sets completed by the least number of respondents to detect significant differences among covariates in our model.⁸⁰ Our draft DCE survey tool (Appendix) will be refined and pre-tested on a local sample of 3-5 providers at the Ann Arbor VA Healthcare System and with our consultants, co-investigators, and Dr. Sriram. We will examine whether providers understand the questions and if the proposed scenarios are realistic. We will modify it accordingly. We will then distribute invitations to the National VA Urology Listserv which includes ~250 VA urologists. We anticipate this survey will be available over the intranet, as an online survey, as well as available in hard copy if preferred. We will use a modified Dillman technique⁸¹ to enhance response rates similar to prior successful survey research.⁸² Our engagement with the National VA Urology Listserv and the AUA Annual Meeting, alongside operational support from the VA Urology Surgery Advisory Board, should engage at least the minimum number of providers needed. If needed, we can pursue other organizations (e.g., AUA, Society of Urologic Oncology) given our prominent urologic oncology team.

C2.2. DCE Statistical analysis

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:

$$Utility = (Constant) + \beta_1 (\text{e.g., physician autonomy}) + \beta_2 (\text{e.g., clinical time}) \dots$$

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 (β_1 , β_2 , 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.

Table 3. Data sources and variables for Aim 2

Information	Source	Variables
Themes, barriers, attributes for discrete choice scenarios	TDF domains and themes related to treating localized prostate cancer with ADT from Aim 1.	4-6 attributes with varying levels (e.g., <i>physician autonomy, clinical time</i>).
Discrete choice experiment	Mixed multi-nomial logit analysis of DCE survey results among national VA urologists	Choice sets, attributes, model outcomes (barrier attribute weights)
Behavior change techniques for most relevant attributes for Aim 3	Michie et al. <i>The Behavior Change Wheel: A Guide to Designing Interventions</i> ⁴⁷	Relevant TDF domains from the DCE model output for use in tailoring strategies

C2.3. Broad intervention categories require tailored design: Formulary restriction & decision-making

There are several potential implementation interventions to de-implement low-value castration within each broad intervention category we identified for this proposal. We focus on formulary restriction and decision-making because of their difference in key attributes, including level (organizational vs. individual), likelihood of quick success vs. long-term sustainment, and effort required by clinicians. We describe some possible intervention design features briefly for each intervention type in Table 4. While several options exist, there is no existing evidence to inform which is the best approach from the provider perspective. Aims 1 and 2 will inform which of these specific approaches is likely to be most acceptable to clinicians, and provide data needed to tailor these broad interventions. For example, we do not know how a blunt formulary restriction intervention would be received by providers considering primary ADT treatment. While formulary restriction of ADT for localized prostate cancer seems warranted, we may find that it is widely considered unacceptable to providers. Nor do we know how shared decision-making can be efficiently operationalized in a clinical setting for patients considering castration for localized disease. By tailoring each intervention strategy using behavior change techniques and barrier solutions derived from Aims 1 and 2, we believe we can design strategies that will be accepted by providers, but still allow us to test differences in the widely varying mechanisms of action. We will refine these approaches through robust efforts in Aims 1 and 2 and the expertise of our trans-disciplinary, multi-site investigative team. For these reasons, qualitative work (Aim 1) and quantitative DCE results (Aim 2) are necessary to refine de-implementation strategies for Aim 3 piloting.

Table 4. Examples of potential pilot interventions	
<i>Formulary restriction</i>	
Prior authorization Oncology consultation Pharmacy review	Used in infectious disease
Criteria for Use EMR order template Selected prescribers	Currently used for restricted drugs
Medication Safety (VAMedSAFE)	Evaluate, educate and prevent adverse events
<i>Decision-making</i>	
Decision aid using a brief in-office pro/con (e.g., Option Grid™)	Commercialized shared decision-making for prostate cancer
Provider training in communication and values elicitation	Evidence-based practice though difficult to implement/sustain
Informed consent for ADT	VA iMed consent

C2.4 Selection and tailoring of formulary restriction and decision-making pilot interventions

C2.4.1 Formulary restriction interventions available in the integrated delivery system

The VA Pharmacy Benefits Management Services uses several tools to encourage optimal use of medications including: 1) National Formulary, 2) Prior Authorization, 3) Criteria for Use, and 4) VA Center for Medication Safety. ADT is currently listed on the VA National Formulary as a standard pharmacy benefit to eligible patients. No prior authorization is necessary to ensure ADT use is appropriate. There are three levels of prior authorization that may be relevant to our tailoring efforts (national, regional, facility). For instance, we could pursue *Prior Authorization* at the facility level if this approach were deemed appropriate with escalation to the region for our subsequent trial. Similarly, we could pursue *Criteria for Use* restriction which is used for other more advanced prostate cancer drugs in VA (e.g., enzalutamide, abiraterone).

These evidence-based restrictions allow authorized providers with expertise to prescribe when indicated with close monitoring for appropriate use. This can be done at the facility-level as in the case of anti-infectives. Alternatively, we could pursue a pharmaco-vigilance policy program given the ADT safety concerns in collaboration with the VA Center for Medication Safety to evaluate, educate and prevent the adverse events associated with castration. Our operational partner, *Mary Burkhardt, MS, RPh, FASHP, FSMSO*, is a national pharmacy expert who is committed to operationalizing our intervention (See letter).

C2.4.2 Tailoring a formulary restriction strategy for ADT de-implementation

It is likely that our formulary restriction intervention will involve refining the current EMR order check template developed and in use by Dr. Shelton and Dr. Skolarus at the VA Ann Arbor to limit inappropriate prostate cancer screening.⁷¹ In general, these templates vary widely across the system, can be made more or less extensive, and can build in limited forms of decision support to specialists prescribing ADT. This is a very flexible, widely used approach, for which the technology already exists and is integrated into the EMR. We will use the taxonomy outlined by Wright et al.⁸⁴ to describe the decision support content and the Template for Intervention Description and Replication (TIDieR) checklist to guide the refinement and tailoring.⁸⁵ For example, when an ADT injection is ordered, a brief interruptive message *tailored* to our prioritized barriers, TDF themes and behavior change techniques (e.g., *persuasion, training, education*), could be shown on the ordering screen. This would allow the provider the option of proceeding or cancelling the order, with or without justification. To ensure this formulary restriction approach was ‘smart’ we would use the following criteria as we begin and explore options during refinement: 1) first injectable ADT order in pharmacy claims (e.g., leuprolide J9217), 2) prostate cancer diagnosis (ICD-9 185, ICD-10 C61), and 3) low PSA level (e.g., levels <20 ng/mL are more consistent with localized disease⁴). We will continue to refine these criteria throughout development with the investigative team. We will vary alert criteria (e.g., age, prior ADT injection) to ensure the number of triggers would be acceptable to providers as done previously. The *tailored* de-implementation strategy will be based on the behavior change techniques corresponding to the most relevant TDF domains from the DCE model (e.g., *education, persuasion, beliefs about consequences, Table 1*). Once we have selected our theory-based messaging, presentation, and approach, we will begin piloting at the VA Ann Arbor and University of Michigan Cancer Center with ongoing refinement (Aim 3).

C2.4.3 Shared decision-making and decision-making interventions to de-implement low value care

Shared decision-making is an increasingly recognized component of high quality care.^{63,73,86} A common model for shared decision-making defines key components as: 1) patient and provider involvement in decision process, 2) sharing of information among parties, 3) consensus building through preference sharing, and 4) patient and provider agreement to implement the decision.⁸⁷ This approach has been associated with less decisional regret and conflict, increased adherence to a treatment plan, empowerment, higher satisfaction with care, and more realistic expectations.⁷³ One relevant example is a randomized trial of shared decision making leading to an absolute 25% decrease in antibiotic use for acute respiratory illness.⁸⁸ Similarly, treatment of localized prostate cancer with ADT is an ideal condition for improving patient-centered care through shared decision-making as chemical castration is not even a guideline recommended option in most cases. Patients have numerous treatment options—observation (i.e., watchful waiting, active surveillance), surgery, and different types of radiation therapy—each with different risks and benefits (e.g., oncological “cure” vs. potential urinary or sexual dysfunction). Unfortunately, many men report low satisfaction with the decision making process and decisional regret. Coupled with wide variation in the use of different treatments such as ADT, this suggests suboptimal decision-making. Moreover, shared decision-making is optimal for situations where there is no best option as often occurs with chemical castration scenarios. However, tools to promote shared decision-making in prostate cancer tend to focus on screening, surgery, radiation and/or observation strategies,⁸⁹ not necessarily ADT for localized disease since it is not recommended care. We plan to explore those patient and provider factors associated with the decision to continue or stop ADT for localized prostate cancer, and believe that ADT is a prime candidate for shared decision-making for at least 2 reasons. First, it is not guideline recommended. Second, there are significant harms that may be under appreciated prior to using a shared decision-making approach therefore decreasing ADT use through our interventions. Therefore, our shared decision-making interventions to de-implement ADT as localized prostate cancer treatment include: 1) Option Grid™ decision aid tool for localized prostate cancer (a brief in-office pro/con discussion handout) (**B9**, Appendix), 2) brief provider training in communication and values elicitation, and 3) informed consent for ADT. Most of these are not routinely used in practice but could decrease ADT use through patient activation. We would consider including information

about the harms of ADT with a focus on alternative treatment options offered in the OptionGrid™ tool. Decision aids are one approach to help patients and providers communicate about their disease and treatment options thereby enhancing shared decision-making and in some cases decreasing overtreatment especially when risks outweigh benefits.⁷³ We could also use an EMR prompt or brief provider training in the principles of communication and values elicitation as another possible approach to improve decision-making. Last, we could enforce rarely used informed consent for ADT which resides in the VA iMedConsent program and explicitly states the indications for prostate cancer spread or metastasis.

C2.4.4 Tailoring the decision-making strategy to de-implement low value ADT

Based on the DCE findings and the experts on our team, we will *tailor* our decision-making intervention for castration with ADT in localized disease. Our extensive experience with the University of Michigan Center for Health Communications Research and its tailored approaches to health care behavior change for Drs. Skolarus' and Hawley's prostate cancer survivorship trial, social marketing in health literature,⁹⁰⁻⁹² and Dr. Sriram, all indicate that, in fact, the way information is presented to both providers and patients in our intervention could lead providers to withhold ADT in the face of risks dramatically outweighing benefits, in addition to perceptions of organizational support to decrease low value treatment with ADT. We have several experts including Dr. Hawley, expert in breast and colon cancer decision-making, Dr. Makarov, Chair of the American Urological Association's Shared Decision-Making White Paper, and marketing expert Dr. Sriram to ensure our intervention is in line with state-of-the-art decision-making and marketing evidence. In addition, we will adhere to the five key steps of any shared decision-making intervention: 1) seeking patient participation in the decision for chemical castration with ADT, 2) comparing treatment options, 3) assessing patient preferences and values for castration, 4) reaching a decision on castration, and 5) evaluating that decision.⁷³ While there is a perception that shared decision-making including preference elicitation takes more time than usual, quantitative data are mixed and its potential benefits warrant implementation especially when it comes to castration.⁷³ For the *tailoring*, we could *model* effective time and personnel strategies to minimize provider time burden in clinic, modify when patients are presented with the information the clinical encounter, and emphasize other strategies (e.g., greater staff involvement) if *clinical time* was found to be a key barrier. Another tailoring option might be brief *education* content directed to the provider if a TDF domain of *knowledge* was identified as a leading barrier. Again, we will select our intervention and theory-based messaging, presentation and approach to pilot in Aim 3.

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

C3.1 Methodological issues to be addressed in de-implementation pilots A well-designed pilot study has many purposes, including testing methods of recruitment; selecting the most appropriate primary outcome; testing acceptability of the intervention by stakeholders; ironing out feasibility and fidelity issues; developing the full study protocol; and estimating sample size for a full trial.^{45,95} As highlighted in implementation literature, preparation and planning are central to successful pilot development and implementation. The need for clear outcomes (e.g., castration rate), systematic, theory-based interventions to change provider behavior (i.e., TDF-driven), and a

timetable are necessary to successfully set up our full- scale evaluation trial. Although it is likely that chemical castration rates among prostate cancer patients will be our primary outcome for the full evaluation trial (# of primary ADT patients with localized prostate cancer / total incident prostate cancer patients), we will also need to consider implementation outcomes (e.g., feasibility) and hybrid study designs. Further refinement in the pilot studies will allow us to explore other outcomes including the total number of ADT injections as we will also be working to stop treatment among those with localized disease who have been continued on ADT. As illustrated in Table 5 below, the piloting of the intervention strategies will focus on 4 major methodological issues.⁴⁵ We will examine issues surrounding recruitment, acceptability, feasibility, scalability, and data collection for the full-scale trial.

Table 5. Methodological issues requiring pilot evaluation prior to a full-scale de-implementation trial

Issue	Assessment	Potential outcome
Recruitment randomization scalability	Monitor proposed recruitment strategy at each facility; check practicality of cluster randomization of facilities; identify issues of participation refusal or withdrawal; acceptability of randomization; number of eligible participants per month; compare clinic flow across recruitment strategies	Select most effective recruitment and randomization strategy; trial messaging to sites; discern patient, provider and cluster sample sizes; refining eligibility screening
Acceptability of intervention	Check acceptability of interventions with urologists and clinic staff at pilot sites; settings for each intervention; consent and documentation practices; tailoring strategies are acceptable; timing of intervention relative to visit	Identify acceptable components of each intervention in clinical practice; consent processes; efficient documentation practices
Feasibility in clinical practice	Assess burden on clinic staff and providers to participate; monitor clinical time and workflow; assess adherence to intervention; technical performance of EMR-based intervention(s); participants representative of those expected in full-scale trial; intervention fidelity	Time and resources needed to roll out in randomized sites; learn research and clinic administrative staff roles for trial; standardization; scheduling practices
Data collection and outcome assessment	Monitor follow up practices for patients on ADT; monitor for asymmetric attrition/retention across intervention sites; missing data; review choice of primary outcome, study design; effect variability	Willingness to participate by intervention preference; effect size; consider hybrid study; duration; full-scale protocol

C3.2 Study populations

We will conduct pilot testing at 2 sites during Years 3 and 4 of this proposal. Dr. Skolarus will lead the pilot efforts at the VA Ann Arbor Urology Clinic, and Drs. Caram and Hollenbeck will lead pilot efforts at the University of Michigan Comprehensive Cancer Center Urologic Oncology clinics. Drs. Shelton, Leppert, and Makarov, each with academic and VA urologic oncology practices, will provide invaluable input into the pilot efforts. The number of patients initiating primary ADT at each site should be adequate for piloting based on preliminary data. However, the primary purpose of the pilots is to assess for issues in Table 5, not effectiveness, so numbers ADT patients are not critical to success for pilot outcomes.

C3.3 Aim 3 data sources and analysis

We anticipate conducting the pilots for a minimum of six months beginning in Year 3. For each pilot, our research team will host a weekly call between Drs. Skolarus, Caram, Hollenbeck, a project manager, RA, Co-I's and consultants to discuss issues. We will audio tape all conference calls, and take field notes during individual calls. At the beginning, we anticipate calls will be longer to deal with barriers and complications. By the end of the interventions, we anticipate that calls will be shorter, and focus more on achievements and lessons learned regarding methodological issues as we prepare for the randomized evaluation trial. We will extract data on ADT use from VA and Medicare data to remain informed about the status of chemical castration as primary treatment across VA and the pilot site. This will allow us to monitor secular trends in performance, and assess possible changes in chemical castration over the pilot period in our pilot site. We will analyze data descriptively, which is most appropriate for pilot studies.⁹⁵ We will use content analysis methods to assess key issues arising from the audio recordings of conference calls and field notes. We will use bivariate analyses (t-test or chi-squared test) to assess the parameters (central tendency and variation) for pilot intervention variables including patient and provider demographics.⁹⁰ In preparation for our cluster randomized trial, we will use national VA data to identify possible sites for Year 4 recruitment.

C4. Timeline

The timeline for this 4-year proposal and submission for a cluster randomized comparative effectiveness de-implementation trial of formulary restriction vs. decision-making is shown here. After the pilot interventions have been refined and tested, we will assess for effectiveness in a cluster randomized trial through a proposal submitted in Year 4. Using a mixed methods approach, the effectiveness of the de-implementation strategies will be assessed from the perspectives of providers and patients. We will plan to field the trial across approximately 20 facilities within the delivery system.

Research Plan	Year 1	Year 2	Year 3	Year 4
Aim 1: Provider and patient interviews, ADT preferences/barriers	█			
D&I: Manuscript and abstract preparation, steering committee		█		
Aim 2: DCE, barrier prioritization, intervention and strategy tailoring		█		
D&I: Manuscript and abstract preparation, steering committee			█	
Aim 3: Pilot de-implementation intervention strategies, IRB			█	
D&I: Manuscript and abstract preparation, steering committee meeting, recruitment for RCT				█
Funding Plan				
Cluster Randomized Comparative Effectiveness Trial (prepare/submit)			█	█

As this research progresses, we anticipate convening a Steering Committee composed of members of the research, clinical, and operations communities, including the VA National Program Director for Oncology, to assess how to optimize the value of castration among prostate cancer patients. This will be critical as these interventions can only be successfully adopted if accepted by local urologists and coordinated with national efforts. By including urology providers across a variety of practice settings (VA, University of Michigan, NYU, Stanford, UCLA), we will keep a broad focus, laying a foundation for transformation of low value castration practices among the prostate cancer community.

C5. Dissemination and Implementation (D&I) Plan

While the ultimate next steps for this work will be a cluster randomized comparative effectiveness trial, setting up this complex trial will create opportunities for dissemination. We will publish at least one manuscript per research aim in peer-reviewed journals, as well as submit at least one abstract to clinical, quality improvement and/or implementation research meetings. We will convene a Steering Committee and update this group through quarterly phone calls as we progress through the research plan. In addition, we will present our findings to the American Society of Clinical Oncology, Society of Urologic Oncology, and the Association of VA Hematology/Oncology as an opportunity to include a de-implementation of low value cancer care theme in their annual meeting agendas. We will brief relevant operational partners annually including the VA National Program Director for Oncology and the VA National Urology Surgery Advisory Board. We will also share our findings and recruit for our cluster RCT at the Annual AUA Meeting.

C6. Project Management Plan

The project management plan will be led by Dr. Skolarus with a project manager and research assistant. It will include weekly research meetings throughout the study duration with conference calls for off-site participants. Dr. Skolarus will be responsible for completion of the research, administrative and regulatory aspects. Dr. Skolarus, and members of the research team, will communicate at least annually with the Steering Committee via telephone and in-person meetings.

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