PROTOCOL COVER PAGE

Protocol Title	Restore: Gay Men and Prostate Cancer Aim III
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ABBREVIATIONS/DEFINITIONS

Include any abbreviations or definitions for key or technical terms you use in your protocol.

- PCa: Prostate Cancer
- GBM: Gay and Bisexual Men
- MSM: Men who have sex with men

1.0 Objectives

Prostate cancer (PCa) is the most common invasive cancer among gay, bisexual, and other men who have sex with men (GBM), with documented disparities, yet it is severely under-researched. Because gay sex differs from vaginal sex, physiologically; the results from 614 studies focused on heterosexual men likely do not generalize to GBM with PCa. This research will advance the field in three ways: First, there have been no rehabilitation studies specific to GBM survivors of PCa, so clinicians have no relevant studies to inform best practice with their GBM patients. Second, most PCa studies have tested only one rehabilitation component. We will conduct the first study of a multi-component, biobehavioral rehabilitation program on quality of life, including both urinary and sexual function. Third, almost all PCa studies have focused on men recently treated for PCa. We will study both men recently treated (last 2 years) and men post-treatment (2+ years), using a stratified design.

The long-term objective of this research is to improve the health of GBM survivors of PCa and to provide an evidence base for rehabilitation. In Aim III, we will evaluate an online rehabilitation program tailored for GBM that addresses both the sexual and urinary effects of PCa treatment. This protocol addresses *Aim III. "To evaluate the effects of a structured online rehabilitation program for GBM PCa survivors".* Note: The recruitment of participants for this study has already been reviewed and approved (see Aim II).

2.0 Background, Significance of Research Question/Purpose, and Existing Literature

PCa is common in GBM, and GBM have poorer outcomes than heterosexual men with PCa. However, there have been no studies to assess the effects of PCa rehabilitation in GBM, and none to assess effects of rehabilitation on gay sex. Our study premise is that structured rehabilitation, tailored for GBM with PCa, will improve their quality of life by reducing the negative sexual and urinary effects of PCa treatment. PCa is the most common non-skin cancer among men, with 180,890 new diagnoses in 2016.[1] Three studies have examined whether sexual orientation and male partners are risk factors for PCa, but results conflict.[2-4]

A recent IOM report concluded "that substantial research is needed" (p.294) to address the health disparities of LGBT persons, citing "cancer rates, risk and treatment (particularly prostate cancer among older gay and bisexual men)" [IOM's emphasis] (p.284) as a prioritized, under-researched area.[5] In our published literature review, we could find only 30 publications regarding GBM with PCa published this century in English, a rate of 1.9 publications per year.[6]

There have been only 5 studies of GBM with PCa with *n*'s>10. The first was a qualitative study (*N*=36) which concluded GBM have little-to-no understanding of the prostate, treatment or sexual sequelae.[7] The second was a Romanian study where 12 GBM reported worse sexual outcomes following PCa treatment than 17 heterosexual men.[8] In the third, 92 GBM reported significantly worse urinary and bowel outcomes, poorer mental health, worse quality-of-life but better sexual outcomes post-treatment than published norms.[9] The fourth found 96 GBM had lower Gleason scores at diagnosis, and more distress at anejaculation, than 460 heterosexual men.[10,11] The fifth (*N*=16)

concluded sexual effects of treatment are particularly "severe" for GBM. While the poor sexual outcomes demand research, the negative impact on quality-of-life adds urgency.[12]

Sexual function is an important component of health[13] and predictor of quality of life,[14,15] including for older men.[13,15,16] While DSM-5[17] defines "sexual dysfunction" as "a clinically significant disturbance in a person's ability to respond sexually", erectile functioning in PCa treatment is typically operationalized as "sufficient for vaginal penetration."[12,18,19] This gold standard is "*irrelevant for gay sex*." [12] Physiologically, anal penetration requires a greater degree of penile rigidity than vaginal penetration[20,21] which may explain poorer sexual outcomes.

There are three main treatments for PCa. *Radical prostatectom*y, the gold standard treatment recommended by 95% of US urologists,[22-24] causes urinary incontinence (UI), total semen loss, and potentially persistent erectile dysfunction (ED).[22] For younger (<60), otherwise-healthy (heterosexual) men *with rehabilitation*, 76% report erections sufficient for vaginal sex within 3 years.[22] GBM may be less likely than heterosexual men to choose radical prostatectomy possibly because of the sexual effects. [25] *Radiation and cryotherapy* have long-term ED outcomes similar to or worse than radical prostatectomy,[26] while also causing chronic rectal complications that may preclude anal sex.[24,27] *Systemic treatment* involves hormonal treatments, usually in combination with surgery and radiation, with worse outcomes. *Active surveillance* is the alternative to treatment, but repeated biopsies can result in ED.[28,29]

For almost all men, PCa treatment negatively impacts sexual functioning,[30-32] sense of masculinity,[30,33,34] and/or self-esteem.[35-38] Erectile dysfunction (ED) and urinary incontinence (UI) are the most common sequelae of PCa treatment. Without rehabilitation, frequent UI is estimated to be 3.3-21%,[39,40] and ED, 40-76% in PCa patients at 2 year post-treatment.[39-41] GBM with PCa face additional challenges including the loss of the prostate as a site for sexual pleasure in receptive anal sex,[24,42] persistent rectal irritation or pain sufficient to prevent receptive anal sex,[12,21] loss of ejaculate (which appears more central in gay sex[43,44]), and climacturia(leaking urine during orgasm) impacting oral sex. Weak erections have been hypothesized to prevent GBM with PCa from following CDC safer sex guidelines, increasing risk of HIV transmission.[45] Some GBM adjust their role-in-sex (from insertive to receptive) to accommodate dysfunction,[10] but this has not been well researched. PCa in GBM intersects with issues of minority status,[43] discrimination,[43] and stigmatization,[35,43] including less familial[42,46-49] and social support,[42,47-49] and less partner involvement in treatment.[42] For HIV+ GBM, HIV treatments and immune deficiency may alter the risk of PCa[24,50-52] and cancer virulence.[24] GBM with PCa have described post-operative sex education as "disingenuous" and "coy" because it never addresses gay sex.[53] Challenges navigating (real or perceived) heterosexual bias in the medical setting[12,42,43,54,55] support groups,[44,54,56] and health systems[42,43] all worsen treatment outcomes[57] and mental health.[9,57] Patient distrust of the medical community[12] and reluctance to disclose sexuality[42,56] are also barriers, with 21% of 2,560 older (50+) LGBT reporting they are not "out" to health providers and 13% reporting homophobic care.[58] In addition, 31% of older LGBT report depression and 40% a history of suicidal ideation.[58] Since older GBM are already at higher risk of depression[59-62] and suicide,[63-68] the lack of PCa treatment studies tailored for GBM is a major concern.

To ensure our structured rehabilitation program is evidence-based and state-of-the-art best practice, we conducted a systematic literature search using “prostate” and synonyms by “sexual rehabil*” “urine”, and synonyms, since 1980, in English, French or Spanish. This yielded 614 references. We highlight three findings. First, of the 614 papers, only 127 (20.7%) focused on rehabilitation. Rehabilitation appears an under-researched area relative to treatment. Second, with few exceptions, research on rehabilitation has focused on UI or ED as separate issues and taken a component approach to studying treatment. But UI and ED often occur together;[69] and are the top two challenges patients ask for help with, online.[70] Combination treatment permits study of both outcomes. We conclude a structured treatment program tailored for GBM is the appropriate first (and next) step in advancing treatment for GBM with PCa.

Many PCa rehabilitation studies equate erectile functioning with vaginal sex; few studies have examined other sexual problems. For example, only two papers have examined climacturia. The first estimated 20% of otherwise continent men experience it after radical prostatectomy, and showed it increased survivors’ sexual anxiety, avoidance of sex, and low orgasmic satisfaction.[71] The second estimated prevalence, 4-years post-treatment, to be 33.9%.[72] No treatment studies have been published or used climacturia as a primary end point, a gap this study will address.

Of the 614 articles reviewed, 612 focused on vaginal intercourse or erections. None were in GBM. There have been no studies (in heterosexuals or GBM) of rehabilitation for insertive anal sex, receptive anal sex, and no studies to treat climacturia. This absence makes it literally impossible for clinicians to practice evidence based medicine with GBM patients. The IOM concludes this failure of science creates and sustains GBM health disparities.[73]

As reflected in the small size of the few published studies, recruitment has been a major barrier impeding GBM with PCa research.[53] Given our success in recruiting the largest sample to date, we are the right team to test new methods for recruitment.

3.0 Preliminary Data

Restore-1, our recently completed R21, is only the second NCI-funded study on GBM with PCa, and the first to reach publication.[74] This study included two cross-sectional components: qualitative telephone interviews (n=30) and an online survey was conducted (n=193) to determine the examine the experiences of GBM with PCa and conduct a needs assessment to inform our current intervention. In qualitative interviews, men described radical prostatectomy as leaving them “humiliated,” “maimed”, “less than other gay men,” and “severely depressed.”[75,76] Most (88%) GBM assessed their sexual functioning as inadequate, post-treatment[77] resulting in poorer mental health,[76] and decreased quality of life (QoL).[77] Clinicians address only 3 of the 8 (38%) treatment effects commonly experienced by most GBM with PCa; leaving most GBM to treat themselves, informally.[78] We found no evidence of any standard of care for rehabilitation,[78] an outcome potentially explained by the lack of science to inform clinical practice. Three (2%) participants became HIV-positive after PCa treatment, raising concerns whether lack of rehabilitation led to condom difficulties and, ultimately, HIV infection.[77] Almost all participants expressed interest in a tailored, online rehabilitation program.[79]

4.0 Study Endpoints/Events/Outcomes

4.1 Primary Endpoint/Event/Outcome:

Health Related Quality of Life; measured as combined scores of the FACT-P and BSI-18 inventories

Sexual function and bother in anal and oral sex; measured via the EPIC-26 inventory and gay sexual functioning inventory

Urinary function and bother; measured via the EPIC-26

4.2 Secondary Endpoint(s)/Event(s)/Outcome(s):

Self-reported climacturia, measured via the Gay Sexual Functioning Inventory, which we are developing for this study.

5.0 Study Intervention(s)/Interaction(s)

5.1 Description:

The intervention includes six primary focus areas:

(1). *PDE5-I drugs:* Participants will be offered the option to take 60mg sildenafil orally, 3x per week for 1 year. Participants for whom it is contraindicated, who are unwilling or unable to get a prescription from their physician, who prefer to use an alternative erection enhancer not covered by our study, or do not wish to take sildenafil will still be included in the intervention.

(2). *Pelvic floor exercises (a.k.a. Kegels):* To strengthen the levator ani muscle, both to treat UI and climacturia, videos and educational materials will demonstrate proper technique for pelvic floor exercises. For climacturia, we will emphasize voiding bladder prior to sex, shaking of the penis; and clenching pelvic floor muscles during orgasm to keep sphincters closed.

(3). *Vacuum pump and* (4) *masturbatory exercises:* Participants will be given a penile vacuum pump and encouraged to use it with masturbation to stimulate blood flow to the penis. In addition, they receive three different sized dildoes to help with receptive anal sex and two penile constriction rings (aka “cock rings”).

(5). *A gay man’s/couple’s guide to sex after PCa treatment:* Our mobile-enabled interactive website will have videos modeling how GBM with PCa deal with sexual challenges (e.g., disclosing PCa to a sex partner); and a male couple discussing how they have good sex, post-treatment.

(6). *Social support:* We will provide participants with a coach to help them in rehabilitation, moderated forums and other opportunities for men to exchange advice and support with peers and experts.

Participants in the intervention group will receive the following:

- PDE5-I drugs. Participants will be given a letter and instructions to obtain a prescription from their doctor. They will then obtain their drugs online or over the phone via our pharmacy partner, Marley Drug. The study will pay directly for sildenafil for all intervention participants.
- A welcome package including a vacuum pump, tension bands and anal dilators (which are recommended tools in the content), and written educational materials (which are also provided in the online intervention).

- Access to a comprehensive online intervention, including written and video educational materials on each focus area, tracking tools to encourage and measure adherence, supplemental educational materials, and moderated forums.
- Regular contact with study staff, who will encourage adherence, provide advice, and answer questions. In addition, participants will have access to monthly expert webinars, with presentations from specialists in prostate cancer and sexual health.

6.0 Procedures Involved

6.1 Study Design:

We will conduct a randomized controlled trial. Participants will be randomized 1:1 to receive either the online intervention or usual care. Treatment groups will be determined via permuted block randomization and will be stratified by relationship status and time since treatment (<2 years vs 2+years) with blocks of four.

6.2 Study Procedures:

Following successful screening (see below), participants will review an online consent form which overview the study, study tasks, outlines risks and benefits, strategies tor educe risks, and risk-benefit analysis. After this, they participate in an initial telephone call from the project coordinator where they have the opportunity to ask any questions and have them answered, as well as verify information for cross-validation purposes. Then, if confirmed eligible and unique, they receive access to the baseline survey. Participants who complete the baseline survey will then be randomized, via a computer assignment, to a treatment or control group.

Participants in the control group will be notified by email. Thereafter, they will be contacted occasionally with survey links and reminders. As needed, additional casual communications will be used to increase retention.

Participants in the treatment group will be emailed immediately with a username and password to access the intervention. They will be mailed their welcome packet within one week.

Surveys will be conducted at baseline, and at 3, 6, 9, 12, 18, and 24 months follow-up. Surveys are attached.

Interaction for all participants in our study will include an online screening survey, a vetting phone conversation, an email confirmation, followed by an online baseline survey and five follow-up surveys. In addition, all participants can contact the study at any time using a 1-800 and/or our study email. In all email and phone contact, we will maintain HIPPA compliant standards to ensure no privacy violations. (e.g., we will not describe the nature of the study in phone or email messages). In addition, data will be maintained in password protected files on a secure server.

6.3 Follow-Up:

Participants will be followed for twenty four months. Participants randomized to the intervention group will have access to the website and forums throughout the two years; however, it is anticipated that participants will experience the bulk of the intervention experiences during the first year. Sildenafil will only be provided for the first twelve

months. All participants will receive follow-up surveys at months 3, 6, 9, 12, 18, and 24 (attached).

6.4 Individually Identifiable Health Information:

Attached

7.0 Data Banking

N/A

8.0 Sharing of Results with Participants

The results of this study will be made available to interested participants through the use of lay summaries posted on our website. Our format is to use executive summaries which report in lay language the main results of the study. In addition, we will email updates, including reports and publications to participants. Participants may choose to opt out of email updates.

9.0 Study Duration

9.1 Describe:

The duration anticipated for an individual participant's participation in the study.
The total duration of participation is 24 months. Follow-up surveys will occur for both treatment and control groups at baseline, 3, 6, 12, 18, and 24 months. For participants in the treatment group, PDE5-I drugs will be provided for 12 months, but the online intervention will be continue for 24 months.

The duration anticipated to enroll all study participants. We expect enrollment to last 13 months from January 2019 through February 2020. The duration anticipated to complete all study procedures and data analysis. The study will take five years total, including 15 months of preparation, 37 months of recruitment and intervention, and eight months for analysis.

10.0 Study Population

10.1 Inclusion Criteria:

Each participant must be:

- An adult biological male who has had sex with a man or men
- Diagnosed with PCa and treated or pending treatment, including but not limited to radical prostatectomy, radiation, and/or hormone therapy
- Recent problems with sexual and/or urinary function
- Living in the United States or its territories
- A unique, validated individual

10.2 Exclusion Criteria:

- Cognitive Impairment
- Non-English speaking/reading
- Patients who underwent a bi-lateral, non nerve-sparing, prostatectomy (for which rehabilitation is not recommended as efficacious).

10.3 Screening:

Participants will complete an online screening survey to evaluate inclusion criteria (attached). Upon completion of the screener, study staff will call each participant to confirm identity, confirm screening survey answers and evaluate English and cognitive proficiency. Participants' IP addresses will be used to ensure US location and deduplication.

11.0 Vulnerable Populations

11.1 Vulnerable Populations:

☐ Children
☐ Pregnant women/Fetuses/Neonates
☐ Prisoners
☐ Adults lacking capacity to consent and/or adults with diminished capacity to consent, including, but not limited to, those with acute medical conditions, psychiatric disorders, neurologic disorders, developmental disorders, and behavioral disorders
☐ Approached for participation in research during a stressful situation such as emergency room setting, childbirth (labor), etc.
☐ Disadvantaged in the distribution of social goods and services such as income, housing, or healthcare
☐ Serious health condition for which there are no satisfactory standard treatments
☐ Fear of negative consequences for not participating in the research (e.g. institutionalization, deportation, disclosure of stigmatizing behavior)
☐ Any other circumstance/dynamic that could increase vulnerability to coercion or exploitation that might influence consent to research or decision to continue in research
☒ Undervalued or disenfranchised social group
☐ Members of the military
☐ Non-English speakers
☐ Those unable to read (illiterate)
☐ Employees of the researcher
☐ Students of the researcher
☐ None of the above

11.2 Additional Safeguards:

This study is designed to address health disparities affecting sexual minority men, so inclusion of GBM is central and essential to the study. Stigmatization is the main concern. Multiple stigmas have been identified in this population, however we have taken care to minimize risk of stigma. With these protecitons, we believe risks will be minimal.

12.0 Number of Participants

12.1 Number of Participants to be Consented:

We plan to recruit 450 participants: 150 participants who have undergone treatment in the past two years and 300 who have had at least two years since their PCa treatment.

We expect 80% power to detect the statistically significantly differences between the intervention group and the control group. The power calculation was based on standardized effect size = 0.35, total number of observations per participant during the course of the study, *M* = 9, total number of participants, *N* = 450, assumed within-subject variability, σ^2 = 0.50, assumed between-subject variability, $\tau^2 = 0.20$ and a linear change over time.

13.0 Recruitment Methods

13.1 Recruitment Process:

Our recruitment strategies, already approved in a separate protocol, will have three arms:

1. Urology Clinics and other Prostate Cancer Organizations: In the spring and summer of 2018, we built relationships with prominent urology and oncology clinics, urologists and other prostate cancer specialists working in private practice, and federally-qualified gay health centers and family practice clinics with large gay patient populations, nationwide. These medical sources will provide recruitment materials, such as letters, email invitations or fliers, to their gay and bisexual patients. Additional recruitment partners in this aim may include prostate cancer support groups or community nonprofit organizations aimed at cancer survivors.
2. Online from Cancer Support Sites: In our preliminary study, we recruited a sizeable portion of our sample through the online community *Malecare*. We will replicate this successful strategy with both *Malecare* and similar organizations providing online support services to prostate cancer survivors.
3. Directly from the GBM community: We will advertise in gay newspapers (eg Washington *Blade)* and in gay men's chorus concerts programs. In addition, we will recruit through organizations designed to serve LGBT seniors, such as SAGE and Prime Timers, and similar organizations which are likely to have large populations of older GBM.

Recruitment procedures are described in detail in approved protocol # STUDY00003361

13.2 Source of Participants: *Describe the source of potential participants, e.g., Research Experience Program.*

For most of our recruitment strategies, participants will self-identify in response to flyers or advertisements. In addition, clinicians may contact GBM patients, as identified by

clinics via electronic medical records, in order to recruit them into the study. This process will be carried out entirely by the partnering clinics who currently have access to these records. Partner organizations will be provided with a media packet that includes materials for both passive (e.g. flyers and posters) and active (e.g. letters) recruitment. Recruitment materials will point participants to an online screening survey. Upon completion of the screener, potential participants will be contacted by study staff via telephone. These recruitment materials are attached.

13.3 Recruitment Materials:

Our media kit includes:

- Flyers and posters
- Online and print advertisements
- Letters to potential recruiting partners
- Letters to potential participants
- Press release
- Infographics

13.4 Payment:

Participants will be paid $50 after completing the baseline survey, and $25 for each subsequent survey (3, 6, 12, 18, and 24 months), for a potential total of $275.

14.0 Withdrawal of Participants

14.1 Withdrawal Circumstances:

Participants found to be fraudulent or ineligible (i.e. participants utilizing false information to enter the study multiple times) or those who become ineligible (i.e. those who experience cognitive decline during the intervention) may be withdrawn from the study.

14.2 Withdrawal Procedures:

Follow-up surveys will be reviewed for suspicious responses. Participants identified as duplicitous will be removed from the study and further follow-up, and their data will not be included in the analysis.

Participants deemed ineligible due to new health concerns or cognition concerns will be removed from the intervention, but will receive follow-up surveys.

Participants identified as ineligible or fraudulent through the course of the intervention (i.e. via information that is shared on a forum) will remain in the study to prevent selection bias, unless there are concerns for their safety.

14.3 Termination Procedures:

N/A

15.0 Risks to Participants

Foreseeable Risks: We have identified potential risks related to the Aim II study protocol:

1. Risk of breach of confidentiality. Participants are asked to complete the survey in private and to guard their confidentiality, however, the researchers have little control over who else can see the participant. We assess this risk as “unknown.”

2. Emotional discomfort with sexual and prostate cancer questions. This survey asks about sexual, bowel and urinary functioning challenges and their impact on sex. These are sensitive areas to be questioned about. While such questions when asked in in-person interviews are potentially embarassing, it is not clear whether the same questions when asked by computer on a survey are experienced as sensitive. Having had over 15,000 GBM complete sexually focused surveys of similar sensitivity, we note only one man to date reported sensitivity concerns sufficient to contact the study. Our experience suggests such concerns may be rare (and possibly overstated for online surveys).

3. Anxiety and risk of being “outed”. Older men, closeted men, and those less comfortable with or more private about their sexuality and/or a diagnosis of prostate cancer may experience anxiety about being “discovered” or “outed” as being gay/bisexual/MSM, living with PCa, or both by some third party, particularly in a recruitment study that involves snowball sampling, public outreach, and communication on sexual functioning. We assess some risk of anxiety as likely.

4. Concern about security of data. Given the potential of any computer system to be hacked, there are concerns in online surveys about security of data. We assess these risks to participants as minimal and have taken steps described below to minimize these risks.

15.1 Reproduction Risks: N/A

15.2 Risks to Others: N/A

16.0 Incomplete Disclosure or Deception

16.1 Incomplete Disclosure or Deception:

N/A. We intend to fully disclose and there is no deception.

17.0 Potential Benefits to Participants

17.1 Potential Benefits:

Participants in the intervention arm of this study may benefit from the provision of intervention materials worth several hundred dollars. These include free PDE5-I drugs for 12 months, the penile vacuum device, three dildoes (which can double as anal dilators), two penile constriction rings, and access to videos, interactive forums by experts, and the opportunity to read rehabilitation materials tailored to GBM. Participants in the control arm will not receive the direct benefits of the intervention; however, they may benefit from increased assessment or attention from study staff.

17.2 Data Management:

Data will be collected via a series of Qualtrics surveys and managed by study staff.

17.3 Data Analysis Plan:

All analyses will be completed in STATA version 12.0. Comparisons between the intervention and control groups and the outcome measures (EPIC Urinary, Hormone, Sexual, and Bowel, as well as FACT-P and BSI-18 scores) will be evaluated using random coefficient modeling. Stratified analyses will be conducted by time since treatment (2+ years vs <2 years) and relationship status. Models may be adjusted for treatment time, relationship status, comorbidities and demographic variables.

17.3 Power Analysis:

We expect 80% power to detect the statistically significantly differences between the intervention group and the control group. The power calculation was based on standardized effect size = 0.35, total number of observations per participant during the course of the study, M = 9, total number of participants, N = 450, assumed within-subject variability, $\sigma^2 = 0.50$, assumed between-subject variability, $\tau^2 = 0.20$ and a linear change over time.

17.4 Statistical Analysis:

See above

17.5 Data Integrity:

In online surveys it is not always possible to restrict the study raising the necessity of having strong de-duplication and cross-validation protocols to detect fraud. Our experience suggests that between 5-99% of online survey reponses may be fraudulent necessitating strong protocols to exclude fake and duplicative surveys. In order to guarantee that each survey respondant is a unique, validated individual meeting our eligibility requirements, participants will undergo a two-step screening process, including both an online screening survey and a telephone vetting conversation. Fraud will also be assessed by monitoring recruitment into the study, watching in particular for suspicious entries (e.g., a sudden large participation may signal a bot attack). During de-duplication and cross-validation, participants' entry time on study, duration to complete the survey, IP address, age, and zip codes are monitored, as well as answers to information that only health professionals and patients with prostate cancer are likely to know (e.g. Gleason score; medications). Surveys that are suspicious are initially flagged for closer manual checking. Where a survey is clearly duplicative, only the first complete survey will be deemed unique. Where a survey is clearly invalid, it will be rejected. Only after a survey has cleared the de-duplicatoin and cross-validation protocol will a participant be paid. Finally, in the event of suspicious responses (between valid and clearly invalid), we will email the participant to request clarification of the issue.

18.0 Confidentiality

18.1 Data Security:

Well-established, state-of-practice, security protocols will be followed. All data will be encrypted, stored on a dedicated server behind a firewall, identifying information will be separated from the data, and all information and data will be accessible only by password to the investigators and their staff. These procedures have proven effective in the prior online studies conducted by this research team.

It will not be appropriate to include a copy of the consent form in participants' medical, employment, or educational records, because we do not have access to those records.

19.0 Provisions to Monitor the Data to Ensure the Safety of Participants

19.1 Data Integrity Monitoring.

Protocols for study procedures, data management, and reporting will be created by the primary investigator in conjunction with study staff. Monitoring of such proceedings will be conducted by the internal methods committee, comprised of the primary investigator, methodologist, and two additional investigators as well as study staff. Reports on data integrity will be presented to this committee quarterly. Reports will include review of data entry and management procedures, recruitment, randomization, participant communication, and surveys. Each report will include notation of adherence to protocols and accuracy of data.

19.2 Data Safety Monitoring.

Data safety will also be monitored and evaluated quarterly by the internal methods committee, as described above. While risks in this study are minimal, adverse events will be recorded as reported. Events related to intervention procedures may include: reactions to PDE5-i drugs, injury related to pelvic floor exercises or pump use, and other adverse events related to the study. Safety data collection will begin as soon as the intervention website is open to participants. Because this study presents minimal risk to participants, we do not anticipate any conditions that will trigger immediate suspension of research.

20.0 Provisions to Protect the Privacy Interests of Participants

20.1 Protecting Privacy:

Interaction for all participants in our study will include an online screening survey, a vetting phone conversation, an email confirmation, followed by an online baseline survey and five follow-up surveys. In addition, all participants can contact the study at any time using our phone number and/or our study email. In all email and phone contact, we will maintain HIPPA compliant standards to ensure no privacy violations. (e.g., we will not describe the nature of the study in phone or email messages). In addition, data will be maintained in password protected files on a secure server.

Participants in the intervention group will also interact with study staff and other participants (in moderated forums). In addition to the safeguards listed above, participants will not be allowed to share personal information (such as full names) on forums, and will be informed of the risks of sharing personal information online.

18.2 Access to Participants*:*

Our research team will not have access to medical records. However, in order to evaluate adherence, safety, and analyze the results of our study, we will collect information about PDE5-i use, prostate cancer treatment and side effects, and other health conditions. This information will be stored on password-protected, secured servers and will only be available to research staff who will use it for these purposes.

21.0 Compensation for Research-Related Injury

21.1 Compensation for Research-Related Injury: N/A

21.2 Contract Language: N/A

22.0 Consent Process

22.1 Consent Process (when consent will be obtained):

Following successful screening for eligibility, each potential participant will be sent an individual link for an online "chunked" consent page. (attached) Participants will view separate screens for each topic, specifically: 1) a description of our funding and researchers, 2) duration, compensation, and expected survey participation, 3) inclusion and exclusion criteria, 4) description of the intervention, 5) description of PDE5-I expectations and procedures 6) confidentiality policies, 7) participant risks, 8) benefits, and 9) contact information and next steps. At each page of the consent form, participants will click to confirm that they understand that page and wish to continue. On a final page, participants will click to confirm that they are eligible and wish to participate.

22.2 Waiver or Alteration of Consent Process (when consent will not be obtained, required information will not be disclosed, or the research involves deception):

N/A

22.3 Non-English Speaking Participants:

Because our study intervention includes English-language written and oral communication, non-English-speaking participants will not be eligible for this study.

22.4 Participants Who Are Not Yet Adults (infants, children, teenagers under 18 years of age):

N/A

22.5 Cognitively Impaired Adults, or adults with fluctuating or diminished capacity to consent:

Cognitively impaired adults will not be eligible for this study.

22.6 Adults Unable to Consent:

N/A

23.0 Setting

23.1 Research Sites:

This study will be conducted entirely online. Participants will reside throughout the United States and will receive the intervention via a comprehensive website, mailed materials, and telephone conversations.

All team activities, including participant communication, intervention activities, and recruitment, will be based at the office facilities of the University of Minnesota Division of Epidemiology and Community Health.

Recruitment of participants will occur throughout the United States. Recruitment locations may include urologists, community groups in Minnesota and throughout the United States, and print and online advertisements. Recruiting urologists may provide printed materials to their GBM patients, with the approval of their local IRB boards.

23.2 International Research: N/A

23.3 Community Based Participatory Research: N/A

24.0 Multi-Site Research

N/A

25.0 Resources Available

25.1 Resources Available:

Our recruitment objectives are more than double the next largest study of GBM with PCa, so it is reasonable to doubt the feasibility of our goals. However, we're uniquely positioned to find participants because we have had the most success to date with recruitment. In addition, an NCI SPRINT grant provided us the structure to build relationships with referring partners nationwide and build the infrastructure needed to meet our ambitions.

26.0 References

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