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Weight management **A**imed to **R**educe **R**isk and **I**mprove **O**utcomes from **R**adical Prostatectomy
WARRIOR

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Nickname: **WARRIOR**

Protocol Synopsis

Title	**W**eight management **A**imed to **R**educe **R**isk and **I**mprove **O**utcomes from **R**adical Prostatectomy
Nickname	**WARRIOR**
Primary Objective	To test the impact of weight management on obesity-driven prostate cancer biomarkers of recurrence and mortality taken at baseline, 1 week prior to surgery, and 6 months after surgery.
Secondary Objective	To evaluate how weight management affects weight loss, body composition, and weight maintenance in overweight and obese men with localized prostate cancer.
Sample Size	40
Summary of Subject Eligibility Criteria	▪ Men undergoing a prostatectomy ▪ Minimum age of 50 ▪ BMI 25-45 kg/m^2 ▪ Minimum 4 weeks lag-time until prostatectomy ▪ Internet access ▪ iDevice* (iPad, iPod, iPad mini, iPhone) *iDevices may be issued by the research team to be returned at the end of the study.
Procedures	Participants will undergo a pre-surgical weight loss intervention prior to scheduled prostatectomy and a 6-month post-surgical weight maintenance program after prostatectomy.
Primary and Secondary Aims	1. Test the impact of weight management on obesity-driven prostate cancer biomarkers taken at baseline, 1 week prior to surgery, and 6 months after surgery. 2. Evaluate how weight management affects weight loss, body composition, and weight maintenance in overweight men with localized prostate cancer. 3. Test the impact of weight management on QoL in prostate cancer survivors.
Statistics	A two-sample t-test will be used to assess the differences in outcomes between the two groups. The significance of within-group differences will be assessed using a paired t-test.

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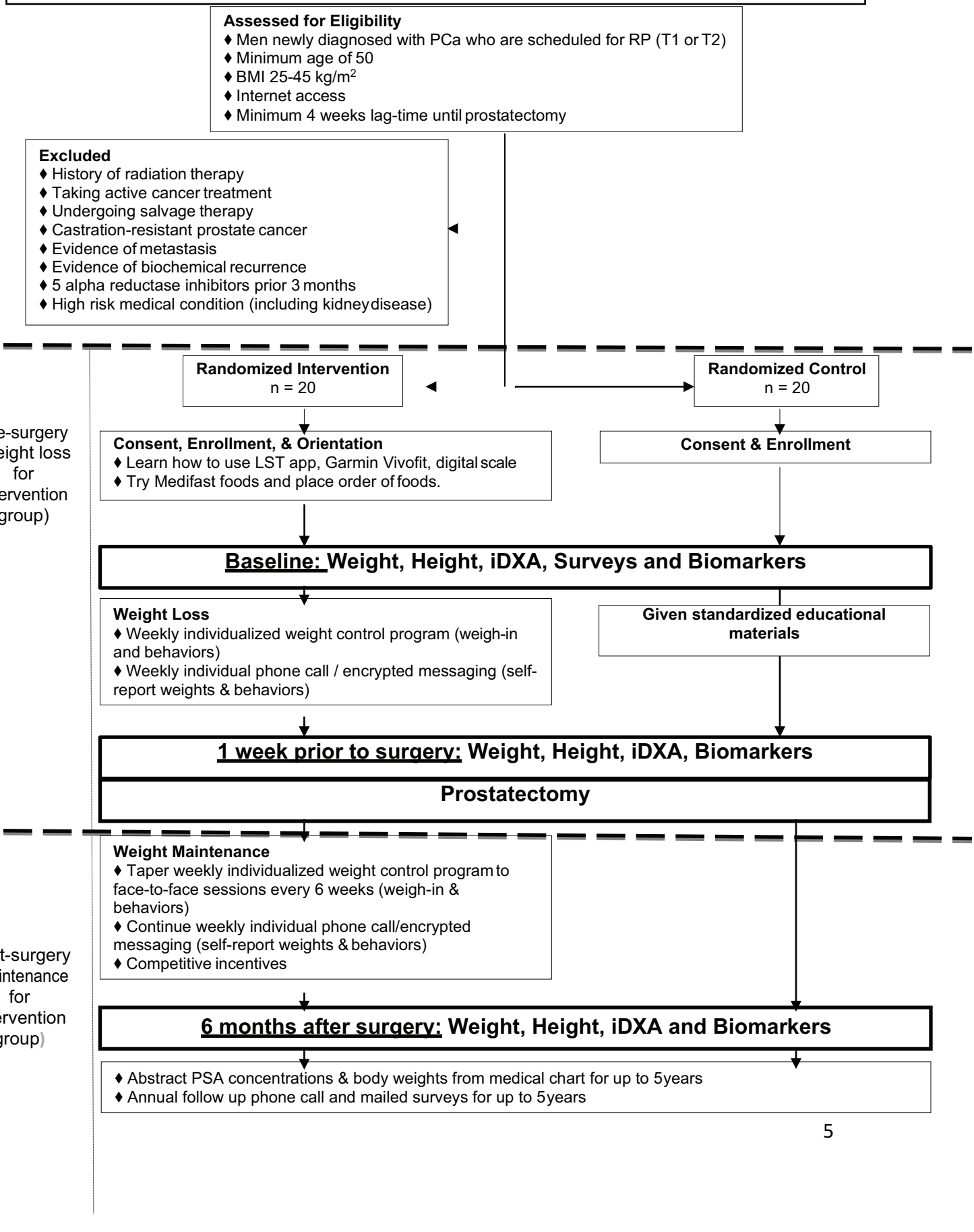
Schema of Intervention: Weight management **A**imed to **R**educe **R**isk and **I**mprove **O**utcomes from **R**adical Prostatectomy, **WARRIOR**



Abstract:

Men who are overweight at the time of prostate cancer surgery are more likely to have their cancer come back than healthy weight men. Healthy weight men also tend to live longer after prostate cancer surgery than overweight men. Fat tissue makes signals that allow cancer to grow and extend beyond the prostate gland, and overweight men have a higher level of these signals. One of the signals is a harmful immune cell that impairs the ability of the immune system to keep cancer in check. Prostate cancer patients with higher levels of these immune cells are more likely to die sooner than men with lower levels of the immune cells. Also, these harmful immune cells use up a nutrient that is needed to produce a signal for penile erection, a common problem after prostate cancer surgery. We think that helping men lose weight before their prostate cancer is removed will help weaken prostate cancer before surgery and prevent it from establishing new tumors in other places in the body. Therefore, weight loss may help prevent the spread of cancer and improve prostate cancer survival and quality of life.

Our goal is to help men live longer after prostate cancer surgery while also improving their quality of life. We would also like to help prevent cancer from ever returning. The aims of our study are: 1) To test how weight management affects weight loss, body fat, muscle mass, and prevent weight regain long-term; 2) To test how weight management affects the harmful immune cells that play a role in cancer coming back; and 3) To test the impact of weight management on two of the major concerns for patients after prostate cancer surgery—urinary incontinence and erectile dysfunction.

We will run a study in 40 patients who are scheduled for prostate cancer surgery. Patients will be assigned to either a weight management program (intervention group; n = 20) or standardized diet and exercise educational materials (control group; n = 20). The intervention group will receive their weight loss program for 4-16 weeks before surgery, while after surgery they will learn additional ways to keep from gaining their excess weight back. The weight management program uses counseling, diet, exercise, and novel, timesaving technology. Measurements will be taken at baseline, 1 week before surgery, and 6 months after surgery for both groups.

Most men with prostate cancer are cancer-free for 5 years after surgery. However, a quarter of them will begin to show signs of cancer coming back after the 5-year mark. Weight management may help support the immune system's role in keeping cancer at bay. Weight loss just before surgery is the optimal time for this strategy to be the most effective. Maintaining the weight loss after surgery is also important to maximize health benefits. Lastly, giving men a weight management program before and after surgery offers them a coping strategy to take steps to improve their health. Our approach will improve the overall health of prostate cancer survivors.

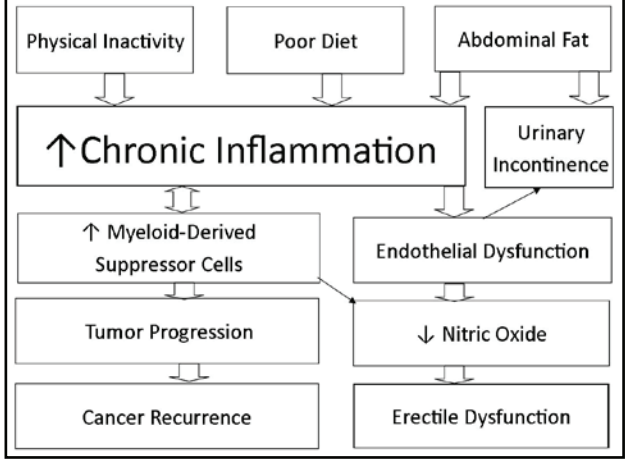
BACKGROUND

Prostate cancer (PCa) is prevalent and treatable, but recurrence and mortality are still problematic. PCa is the most common cancer in men.[1] Although most men with localized PCa are cancer-free for 5 years after RP, 20-30% of these men will begin to show signs of recurrence after the 5-year mark.[2, 3] Moreover, PCa is the second leading cause of death in American men.[1] Since PCa can be slow to grow after initial treatment, a low-risk, high impact intervention to slow the trajectory of recurrence and death is a critical need.

Immune suppressive factors lead to PCa recurrence and death. Myeloid-derived suppressor cells (MDSCs) play a crucial role in cancer-induced immune dysfunction by establishing an immune suppressive environment in prostate tumors.[4] High levels of MDSCs are associated with a shorter survival in PCa patients.[5] Furthermore, MDSC frequencies correlate with PCa stage.[6] Prostate tumors express high concentrations of pro-inflammatory cytokines and MDSCs,[5] which lead to immunosuppression thereby making it more difficult for the immune system to keep cancer in check.[7] Interestingly, the monocytic MDSC subtype is predominant in the blood of patients prior to RP when the tumor is present, but the frequency of the monocytic MDSC subtype decreases after the tumor is removed .[8] Furthermore, our team routinely measures MDSCs in patients before and after cancer surgery.[9] Our pilot data show reduced total and monocytic MDSCs in the weight management intervention ($P = 0.09$; $P = 0.17$, respectively), and the changes in these cell frequencies were different compared to the prospective controls before RP ($P = 0.06$; $P = 0.17$, respectively). We also found that the monocytic MDSC frequencies decrease substantially after RP, but total MDSCs and Tregs do not change with the removal of the tumor. These observations support that the intervention timing is ideal to evaluate the effects of weight loss on tumor-mediated immunosuppressive mechanisms in the peri-operative time frame.

Chronic inflammation leads to PCa progression. Oxidative stress generated from a poor diet and lifestyle leads to genome instability and mutation,[10] and an influx of inflammatory cytokines triggers tumor promotion.[11] Elevated inflammatory cytokines, Interleukin (IL)-8, Tumor Necrosis Factor-alpha (TNFα), and Monocyte chemoattractant protein-1, are implicated in the progression of PCa.[12] Our project will measure all of these cytokines in a multiplex assay to determine if an anti-inflammatory signal is present systemically. Moreover, the CXCL12/CXCR4/CXCR7 signaling axis is centrally involved in tumor progression and recruiting the accumulation of MDSCs to the tumor microenvironment.[13] Therefore, we will measure serum chemokine CXCL12, which is known to be detectable in PCa patients.[14, 15] CXCL12 is an adipocyte-derived factor known to be elevated in obesity, but it is unknown if losing weight will reduce plasma CXCL12 or prostate tissue expressions of either CXCL12 or its receptor, CXCR4. Consultant, Dr. John DiGiovanni has shown that the CXCL12/CXCR4/CXCR7 signaling axis in the prostate tissue is responsive to caloric restriction and will inhibit PCa progression in the HiMyc mice mouse model.[16] These results are promising and exciting, and have informed our premise to test the effects of weight loss on the same signaling axis in human prostate tissue.

Figure 1-Conceptual Framework



Microbiome signature is a potential biomarker. Microbial population present in the human system located in various anatomical sites plays a significant role in human health[17, 18]. Microbiome is a very dynamic structure reflecting the health status and has the potential to be used as a biomarker when characterized and evaluated to a particular disease setup. Alterations of microbial composition is known as dysbiosis and is observed in various disease conditions such as chronic inflammatory diseases and cancers make it a candidate biomarker in health monitoring. Diet and lifestyle are the major factors affecting the composition of the microbial population and thus affecting the metabolic potential and nutritional status[19, 20]. Recent research on prostate cancer research identified alteration of microbiome in the gut, urine and, prostate tissue [21-26]. Identifying the changes in microbiome composition in prostate cancer will be helpful in predicting the prognosis of the disease and when validated may serve as a non-invasive method to predict the disease status. It is of great importance to identify the changes in microbiome in this study setting of prostate cancer patients undergoing surgery with and without weight loss management, diet and lifestyle changes. The outcome from this study will help in identifying the microbial groups associated with weight loss through healthy diet and active lifestyle as well as those are altered after the prostate surgery. The findings will also help in designing diet changes to balance the nutritional status and enable future research in understanding the metabolic changes associated with prostate cancer.

Excess Adiposity and Dietary Factors contribute to an Immune Suppressive Environment and Chronic Inflammation. Obesity-associated inflammation is widely accepted as an important component in cancer progression.[27] Obesity perturbs the tumor microenvironment to favor PCa progression.[28] Excess adiposity is associated with altered immune cell function in obese humans compared to healthy weight humans.[29] Obesity also promotes MDSC accumulation in tumors,[30] which may be triggered by chronic inflammation and insulin- resistance,[31] see **Figure 1**. Neutralizing chronic inflammatory conditions decreases MDSC frequencies and immunosuppressive functions.[32] Modulating inflammatory pathways in the tumor microenvironment may slow obesity-driven PCa progression. Excess visceral adiposity is associated with adipocytes promoting the spread of cancer outside the prostate gland, and the inflammatory and immune suppressive secretions of the adipose tissue surrounding the prostate gland are viewed as a crucial to PCa progression.[33] Obesity increases secretions of chemokine, CCL7, known to contribute to the spread of PCa.[33] Excess body fat leads to elevated inflammatory cytokines, locally and systemically.[34]

A weight loss intervention has strong potential for reducing inflammation and immune compromise. Weight loss reduces inflammation within a short time frame as evidenced by a 16-week program significantly reducing inflammatory IL-6, leptin, and CRP.[35] Moreover, ≥5% weight loss in men prior to a RP altered the gene expression of CXCR4, CXCL2, and insulin-like growth factor 2 receptor in prostate tissue.[36] Another pilot study by the same group showed modest weight loss in a study of caloric restriction in men prior to a RP and reported a beneficial increase in insulin growth factor binding protein 3.[37] Our pilot data show an average 6 kg of weight loss (95% CI, 3-8 kg; $P < 0.001$) and 4 kg of fat loss (95%CI, 2-6 kg; $P<0.001$) reduced MDSC counts, and improved cardiometabolic profiles. However, we do not yet know the effects of weight loss on targeted obesity-driven immune cells and inflammation/chemokine markers in an adequately powered RCT.

Our project will test the impact of weight management on urinary incontinence and erectile dysfunction. After RP, obese men have higher rates of erectile dysfunction [38, 39] and urinary incontinence [39-42] than normal weight men. Weight loss interventions show benefit to both improved erectile function [43, 44] and urinary continence in obese men.[44] Urinary incontinence and erectile dysfunction are two of the major concerns for patients after radical RP. Poor general health, in addition to bother due to urinary and sexual dysfunction, has been found to be an independent predictor for regret after RP.[45] Abdominal adiposity is associated with urinary incontinence, and our pilot data show that the men on the weight loss intervention reduced waist

circumference (P = 0.004) and visceral adipose tissue (P = 0.003) from baseline to 1 week prior to surgery. Erectile dysfunction in obese men is attributed to endothelial dysfunction and low nitric oxide bioavailability due to chronic inflammation and insulin resistance, while physical activity and nutrition have been recognized factors to influence vascular nitric oxide production, reduce chronic inflammation, and thereby improve erectile function.[46] Our pilot data show that total MDSC counts are responsive to weight loss. Moreover, our results suggest that the reduction in total MDSC counts remain stable during weight maintenance. Interestingly, MDSCs express and release arginase-1, depleting plasma arginine concentrations.[47] Arginine acts to increase the production of nitric oxide, a major mediator of penile erection. We think that reducing MDSCs may allow more arginine availability to produce nitric oxide, thereby improving erectile function. We will evaluate if weight loss *before* the critical timing of RP and weight maintenance *after* RP can counteract the harmful effects of obesity on urinary and sexual qualities of life one year post-RP as measured by the Expanded Prostate Cancer Index Composite (EPIC) Instrument-26. Our randomized, clinical trial will help estimate the number of participants needed to detect significant differences in QoL measures as a tertiary objective.

INNOVATION

Our scientific premise is that weight management has high potential as an effective and low-risk strategy to reduce obesity-driven PCa progression and improve the QoL of patients with PCa who undergo RP. The proposed associative mechanistic work will make the field better by evaluating a potential solution to obesity-driven PCa progression. Data suggest that weight loss decreases inflammation and improves insulin sensitivity, but the effect of weight loss on the specific immune cell types known to mediate PCa progression is completely unknown. Filling this gap is critically important since these immune cells are the primary drivers of the inflammation that influences PCa progression.[4] Our contribution will evaluate mechanistic targets and will test a potential strategy to disrupt the obesity-cancer link. The concept is *novel* because our team was the first to discover that weight loss lowers myeloid derived suppressor cell frequencies.[9] This effect may be associated with meaningful clinical outcomes: dampened local inflammation, decreased progression, and improved QoL. However, the therapeutic implications of our work need an adequately powered RCT and associative mechanistic work as we are proposing.

SIGNIFICANCE

To date, only three pilot weight loss interventions prior to RP have been conducted, reporting modest weight loss.[36, 37, 48] Key knowledge gaps remain.

- Changes in body composition and weight maintenance after surgery have not been reported in this population.
- A comprehensive program including all pillars of successful weight management programs such as a reduced calorie diet, exercise, and behavior change components tailored to men has not been tested in men scheduled for RP.
- Strategies to offset the pro-cancer effects of obesity are desperately needed. Weight loss is a promising strategy to alter the immune cells that are driving the inflammatory processes that lead to PCa progression, but it has not yet been tested in an adequately powered RCT.

Our project will test the impact of weight management on obesity-driven immune and inflammatory biomarkers for PCa recurrence, death, and QoL. Our translational approach stands apart from other trials, since we still know very little about how weight management prevents poor PCa patient outcomes and how weight management at a crucial time before surgery influences recurrence, survival, and QoL.

Weight management in men is less commonly studied. Most weight loss programs target women, while behavior change interventions in men are limited. Data suggest that men respond better to a program emphasizing *competition, autonomy, technology, cost savings, and male-specific values or barriers to change*.[49] Our approach weaves all of these themes into a program shown to be effective in men with PCa.

PRELIMINARY STUDIES

The underpinning of this study is based on a pilot trial testing the feasibility of the weight management intervention tailored for men with localized PCa (ClinicalTrials.gov Identifier: NCT02252484). We enrolled 20 overweight and obese individuals (20% African American men). Participants have an average body mass index of 30 kg/m^2 and an average age of 60. Our pilot demonstrates that the weight management intervention:

- Is feasible within our proposed timeline since we enrolled 20 participants in eighteen months;
- Leads to 6 kg of weight loss (≥5.4% body weight) before surgery (95% CI, 3−6 kg; P < 0.001);
- Reduces total body fat by 4 kg (95% CI, 2−6 kg; P < 0.001);
    - Reduces visceral adipose tissue (P = 0.003),
    - Reduces waist circumference by 5 cm (95% CI, 2-7 cm; P = 0.004)
- Improves insulin-sensitivity
    - Reduces fasting blood glucose by 11 mg/dL (95% CI, 0.5−22 mg/dL; P = 0.04);
    - Reduces fasting insulin by 3.4 µIU/mL (95% CI, 0.1−7 µIU/mL; P = 0.03);
    - Reduces C−Peptide by 0.7 ng/L (95% CI, 0.17−1.3; P = 0.01);.
- Reduces total MDSCs (P = 0.06); and monocytic MDSCs (P = 0.17) before surgery.
- Twelve weeks after surgery, weight was maintained and physical quality of life was better in the intervention group than the non-intervention group (P=0.03).

Therefore, our approach with a simple meal replacement plan, well-trained coaches, and novel, time-saving technology moves the field a step closer to a practical clinical care approach and associative mechanistic work to better understand the important problem of obesity-driven PCa progression.

AIMS AND HYPOTHESIS

Men who are overweight at the time of radical prostatectomy (RP) are more likely to have recurrence and die from prostate cancer (PCa) than healthy weight men.[50-52] Men who gain additional weight after RP are also at increased risk of recurrence.[51-53] Obesity exacerbates immune suppressive factors associated with PCa progression [28, 31] and death. [5] Conversely, weight loss may reduce immune suppression at the site of the tumor and help prevent the spread of cancer outside the prostate gland. Weight loss *prior* to RP could be the optimal time to influence PCa prognosis. Research conducted in our laboratory found that a weight loss intervention administered prior to surgery led to 6 kg of weight loss (95% CI, 3-8 kg; P < 0.001) and 4 kg of fat loss (95%CI, 2-6 kg; P < 0.001) from baseline to surgery (mean = 6.6 weeks) among 15 overweight men. Moreover, the intervention reduced immune suppressive myeloid derived suppressor cells (MDSCs) in our weight management arm before RP compared to the prospective control arm. It remains unclear how weight loss affects other obesity-driven biomarkers of PCa progression, urinary outcomes, and sexual outcomes which are all important for better survival and quality of life (QoL). There is a critical need to examine the effects of weight loss on immune profiles, inflammation response, and QoL in order to determine whether large-scale trials of weight loss to enhance PCa survivorship are justified to disrupt the obesity-cancer link.

Our long term goal is to improve PCa prognosis, survival, and QoL after RP. The primary objective of this application is to assess the impact of weight loss *before* and weight

maintenance *after* PCa surgery on obesity-driven PCa biomarkers. Forty men with stage T1 or T2 PCa scheduled to undergo RP will be randomized to receive a weight management program (intervention; n = 20) or standardized education materials (control; n = 20). Our pilot work has established that men awaiting RP are very motivated and embrace the pre-surgical intervention as a means to cope with anxiety by improving their health. We employ a weight loss intervention that emphasizes competition, autonomy, technology, cost savings, and male-specific barriers to change—factors that prior studies have found to be important to successful weight loss interventions among men. We also examine critical QoL factors that could affect the feasibility of the intervention in future trials and clinical practice. Our hypotheses and specific aimsare:

1. ***To test the impact of weight management on obesity-driven PCa biomarkers taken at baseline, 1 week prior to surgery, surgery and 6 months after surgery.**
   - *Hypothesis 1.1:* Immune suppressive factors will respond to the intervention with reduced total MDSC (Lin- CD11b+ CD33+) and monocytic MDSC (Lin- CD11b+ CD33+ CD14+ CD15-) counts compared to baseline values and to the control group. ***Primary Objective**
   - *Hypothesis 1.2:* Participants in the intervention group will have a more favorable chemokine, adipokine, and cytokine profile than the participants in the control group.

2. **To evaluate how weight management affects weight loss, body composition, and weight maintenance in overweight and obese men with localized PCa.**
   - *Hypothesis 2.1:* The intervention will lead to significant weight reduction compared to the control group from baseline to 1 week prior to surgery.
   - *Hypothesis 2.2:* The intervention will reduce body fat and maintain lean body mass as measured by Dual Energy X-Ray Absorptiometry (iDXA) scans from baseline to 1 week prior to surgery.
   - *Hypothesis 2.3:* The intervention will lead to weight maintenance (<3% regain) 6 months after RP.

3. **To test the impact of weight management on QoL in PCa survivors.**
   - *Hypothesis 3.1:* The intervention will report better urinary function and lower urinary bother compared to control 6 months after RP as measured by the Expanded PCa Index Composite (EPIC) Instrument-26.
   - *Hypothesis 3.2:* The intervention will improve sexual function and QoL 6 months after RP as measured by the EPIC-26.

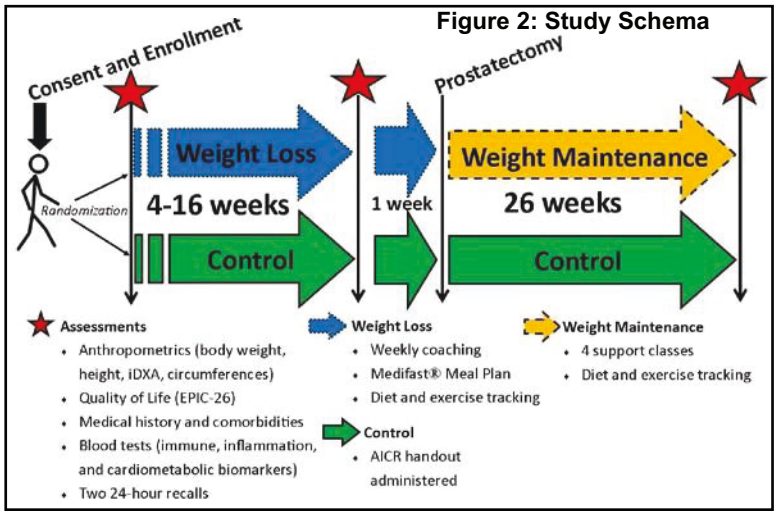
4. **To test the impact of weight management on gut microbiome composition at base line, prior to surgery and 6 months after surgery.**
   - *Hypothesis 4.1:* The intervention will provide the knowledge of dominant microbial populations before and after weight management.
   - *Hypothesis 4.*2: The intervention will also identify the microbial populations that are altered by surgery.

Impact. Weight loss prior to RP may offer a low risk, high-impact means of protecting against PCa progression. Data suggest that weight loss decreases inflammation and improves insulin sensitivity, but the effect of weight loss on the specific immune cell types known to mediate PCa progression is completely unknown. Filling this gap is critically important since these immune cells are the primary drivers of the inflammation that influences PCa progression. Our multidisciplinary research team is uniquely qualified to successfully conduct the proposed study. This project will determine whether weight loss can alter obesity-driven PCa biomarkers and will lay the groundwork for a definitive multi-site trial to test the effects of weight loss and biomarker changes on PCa recurrence, QoL, and survival.

RESEARCH DESIGN AND METHODS

AIM 1: Test the impact of weight management on obesity-driven PCa biomarkers taken at baseline, 1 week prior to surgery, and 6 months after surgery.

Figure 2: Study Schema



We aim to assess the effect of a novel weight loss intervention before and weight maintenance intervention after PCa surgery on obesity-driven PCa biomarkers. We will measure obesity-driven PCa biomarkers, body weight, body composition, and urinary/sexual QoL at baseline, 1 week prior to RP, and 6 months after PCa surgery (See **Table 3: Schedule of Evaluations**). We will test the proposed objectives in a randomized, clinical trial providing either a weight management program (intervention group; n = 20) or standardized educational materials (control group; n = 20) to forty men with stage T1 or T2 PCa planning to undergo RP (See **Figure 2: Schema, Experimental Details**). We will use permuted block randomization. Patients will be assigned to one of the two treatment groups using a randomization list created by the statistician. The randomization scheme will assure that the groups are balanced at every block of 10.

All participants will receive a book, “Dr. Walsh’s Guide to Surviving Prostate Cancer” by Patrick C. Walsh and Janet Farrar Worthington and a booklet from the American Institute for Cancer Research, “Heal Well, A Cancer Nutrition Guide”. Participants randomized to the intervention will undergo the weight loss program for 4-16 weeks prior to surgery and a weight maintenance program for 26 weeks after surgery, while patients randomized to the control group will only receive the book and booklet at baseline. The same assessments will be measured and analyzed in all participants at the clinic visits at baseline, 1 week prior to surgery, and 6 months post-operation. Major deviations from the protocol will be recorded. However all evaluable patients will be analyzed according to intention to treat.

Participants. Overweight or obese men scheduled for RP with newly diagnosed PCa will be recruited from the University of Kansas (KU) Hospital Urologic Clinic and the KU Cancer Center (See **Table 1**). The Department of Urology at the KU Medical Center is the only academic urology program in the region performing 477 prostatectomies over the past 2 years. Co- investigator, J. Brantley Thrasher, MD, is the co-director of operative services. Our recruitment goal is 1 participant per month. Dr. Thrasher or his team of urologic surgeons will describe the study to candidates for RP and provide the name and medical record number of interested patients to Dr. Hamilton-Reeves’ study team. Patients with newly diagnosed PCa will be offered entry into the trial during the discussion of radical RP which typically has a waiting period anywhere from 4-16 weeks from consult to scheduled surgery. Our pilot data in the RP population show 80% are White; 20% are Black/African American (AA); and 10% are Hispanic men.

Table 1: Inclusion/Exclusion Criteria

Inclusion Criteria	Inclusion Justification
Men newly diagnosed with PCa who are scheduled for RP (T1 or T2)	Assure intervention is aimed at a targeted population to reduce heterogeneity
Minimum age of 50	Lower age limit to minimize aggressive cancer phenotypes
BMI 25-45 kg/m2	If men drop to a BMI of 22, they will be routed into the maintenance phase of the intervention.; upper limit for feasibility for iDXA measurements
Internet access*	Assure access to daily diet/physical activity tracking viewed by participant and weight loss coach
Exclusion Criteria	**Exclusion Justification**
History of 5 alpha reductase inhibitors prior 3 months	Avoid confounding effects of treatment
History of radiation therapy for cancer treatment	"
Taking active cancer treatment	"
Undergoing salvage therapy	"
Castration-resistant PCa	Avoid harm to patients with a poor prognosis or altering their course of treatment
Evidence of metastasis	"
Evidence of biochemical recurrence	"
High risk medical condition (e.g. kidney disease, uncontrolled diabetes, etc.)	"

*If patients do not own a compatible device the study team will loan a device to be returned at the end of the study

AIM 2: Evaluate how weight management affects weight loss, body composition, and weight maintenance in overweight and obese men with localized PCa.

Study Intervention components: The cornerstone of weight management for overweight and obese adults is a comprehensive program, which includes a reduced calorie diet along with exercise and behavior change components.[54] Our weight management program is designed to help participants lose ≥5% of their body weight before their RP and to help them maintain that weight loss after their surgery. This goal can be challenging, yet we find that men scheduled for RP are highly motivated. However, the motivation wanes after surgery. Although our four-component intervention may at first glance seem complicated, our approach is actually very simple as demonstrated by the 90% retention in our pilot study.

Behavior therapy/Coaching: Face-to-face coaching sessions are used to discuss progress, overcome obstacles, make adjustments to the diet and exercise regimen, and learn diet and exercise strategies for cancer survivorship. Before the surgery, the one-on-one coaching sessions occur weekly. After the surgery, 4 coaching sessions are given every 6 weeks in a setting with other study participants, spouses/caregivers, and the coach. Coaches are trained as health educators with credentials as either personal trainers or dietitians working under the supervision of Dr. Jill Hamilton-Reeves who is also board-certified in oncology nutrition and certified as a personal trainer. Patients and coaches also connect within the app for real-time monitoring and reinforcement. The dashboard on the app shows body weight to reinforce self-efficacy and accountability.

Diet: The Medifast® 5 & 2 & 2 meal plan simplifies the goals of eating more vegetables, less sugar, 25 grams of soy protein (via meal replacements), and reduced red meat. The meal plan is based on the diabetic exchange system and allows participants to tally food groups for lean proteins, healthy fats, healthy snacks, greens (non-starchy vegetables), and 5 meal replacements (shakes, bars, low-calorie pre-packaged meals) each day. The plan emphasizes the importance of eating at regular time intervals, consuming high-volume, low-energy dense vegetables and reducing problematic snacking. Food intake is tracked through the app with a seamless interface into the USDA food database. The app tallies each food group to reinforce self-efficacy.

Physical activity: An accelerometer is used to track steps. Extra exercises are added to the participant's plan based on the participant's goals and progress. Short exercise videos created by our team are loaded within the app to help participants remember the exercises. The exercise videos include prompts to remind participants of proper biomechanics. The overall physical activity goal is ≥150 minutes of intentional exercise per week and slow progression to ≥10,000 steps/day through increasing activities of daily living. Activities are tracked through the app by logging intentional exercise and syncing the accelerometer. The dashboard on the app shows daily steps and ranks participants on a leaderboard to help motivate the participants.

Technology and Tracking: Participants keep track of their body weight, diet, and physical activity in LifeScience Technologies (LST) AtHome, an app co-designed by our team and LifeScience Technologies. Daily tracking within the LST AtHome app helps motivate behavior change through accountability and competitive incentives. The research staff can view data in real time and can communicate with participants through secure messaging to keep participants on track. The secure messaging platform complies with HIPAA encryption requirements by encrypting the data both at rest and in transit, making the data unreadable, and unusable if the communication is intercepted or accessed without authorization.

Receive diet/exercise educational material: Participants will receive a book, "Dr. Walsh's Guide to Surviving Prostate Cancer" as well as a booklet from the American Institute for Cancer Research, "Heal Well, A Cancer Nutrition Guide".

Behavior therapy/Coaching. The intervention includes weekly face-to-face meetings for 60 minutes with specific objectives, key take home messages, and activity assignments (**Table 2**). Individual sessions are needed to accommodate the timing of each participant's scheduled surgery. Since data suggest increasing physical activity, reducing portion sizes, and less frequent eating out account for most of the weight lost in interventions for men,[55, 56] we target these behaviors. Participants' spouses are invited to attend these sessions because data suggest that they influence eating and physical activity habits.[57] Each session consists of a standard protocol to: 1) obtain weight; 2) evaluate compliance to the diet protocol; 3) discuss physical activity; 4) evaluate progress/barriers; 5) provide education based on the curriculum; 6) set goals; and 7) confirm the next appointment. Patients attending sessions from a distance through teleconferencing complete the same protocol with the exception that the weights are obtained from the wireless scale rather than by a health educator in the clinic. A mid-week check-in is accomplished with all participants by a phone call and consists of a scripted check list to track progress, reinforce goals, discuss weight trends, reinforce the weekly education, and discuss strategies to overcome obstacles.

Table 2: Curriculum Tailored for Men with Localized Prostate Cancer (6th grade reading level)

Curriculum for WARRIOR Surgery: Weight loss before Surgery (4-16 week individual program)

Lesson	*Objectives*	*Key Messages*
Overview • Nutrition 101	Define the link between obesity and PCa, taste & order meal replacements; setup technology, basics of nutrients, food labels, grocery shopping	Wear and sync accelerometer; Start tracking nutrition, physical activity, and weight, understanding of basic nutrition
Baseline • Energy Balance/Density • The Medifast 5 & 2 & 2 Plan® • SMART Goals	Show principles of energy balance/density, Personalize the Medifast® 5&2&2 Plan, Self-Monitoring (goal setting that are SMART)	Eat less; increase physical activity; identify personal barriers & potential solutions List foods that you prefer in each food group; identify personal barriers & potential solutions to following the meal plan
• Fuel Your Fight	Define benefits of fruits & vegetables, Identify foods high and low in energy density	Identify favorite fruits and vegetables; plan strategies to increase daily consumption of non-starchy vegetables and fruits, develop strategies for controlling portions
• Physical Activity: FITT	List ways to increase physical activity using Frequency, Intensity, Time, and Type & the difference between usual and intentional activity	Plan ways to increase intentional physical activity over usual activity; identify personal barriers & potential solutions
• Staying Healthy Away from Home	Meal planning, review strategies to limit intake when eating out or in social situations	Identify meals that fit the meal plan at favorite restaurants, recognize what to do in social situations that may sabotage efforts towards weight loss
• Strategies for Success	Identify positive and negative thought processes which could interfere with weight loss	Identify personal barriers & potential solutions, learn how to use positive thinking to stop the vicious cycle
• *Individualized topics*	*Weight loss and increased physical activity*	*Strategies/coaching on individual topics/areas of participant need*

Curriculum for WARRIOR Surgery: Weight Maintenance After Surgery (26 week group support program)

Lesson	*Objectives*	*Key Messages*
Shaken, Not Stirred	Identify sugary beverages; define empty calories Choose fluids using good, better, best guides.	Limit added sugars & alcohol, read food labels Consume ≤ 1 sugary beverage/day
Eye of the Tiger	List physical activity guidelines Choose exercise plan and record it Fuel activity without undoing workout	Exercise increases energy expenditure Exercise ≥ 30 minutes/day
Veg out	Describe and limit energy dense foods Identify foods high in phytochemicals Choose your vegetables and fruits	Consume ≥ 5 servings vegetables & fruits/day
Where's the Beef	List how red, processed, or charred meat affects health Make healthy choices at restaurants Choose your protein	Choose lean chicken, fish/seafood, plant proteins Make ¼ of the plate protein Follow healthy choices guide for dining out

By applying the cultural tailoring framework developed by Resnicow,[58] our intervention materials represent male characteristics in images and wording as well as reflecting the values and barriers perceived by men. The behavior-based program is grounded in social cognitive theory,[59] problem-solving theory, and relapse prevention. The behavioral strategies use key elements within social cognitive theory.

Intervention fidelity. Fidelity will be assessed by comparing session themes with a checklist of basic intervention components (weigh in/tracking progress, diet recall, progress/barriers, education, goal setting, incentives, confirm next appointment) to determine if the intervention was delivered as intended. The PI will observe sessions once every 6 weeks to determine if the specified themes are being addressed. A score greater than or equal to 80% will be considered acceptable. The PI will train staff and will review the fidelity check with each health educator to correct or help improve the program delivery.

Videoconferencing via Zoom. Greater face-to-face contact improves efficacy in men-only trials. Our co-investigators have shown great success with phone counseling,[60, 61] but our years of GU clinical and research experience have found that men demonstrate more non-verbal communication of obstacles and perceived barriers that are critical to identify for more precise psychosocial support. Videoconferencing is supported by telemedicine using the Zoom platform. Videoconferencing will be available to all participants to reduce the burden of the study. We anticipate that participants in rural settings, those traveling from a long distance, or those traveling for work or pleasure will use this option for coaching sessions.
Our pilot study used this option and no issues or problems occurred with connectivity or ease of use.

Daily weight tracking with Carematix® Scales. Daily weighing improves self-monitoring and the adoption of changed behaviors for weight management.[62] Intervention participants will receive a Carematix® scale that seamlessly reads into the app facilitating reinforcement or feedback (help from the health educator if falling off-track). The Carematix® scales will also provide monitoring for those receiving coaching primarily through videoconferencing.

Competitive incentives. During the study, a leaderboard on the app dashboard shows participants their rank for cumulative steps taken, participants are listed by aliases to protect identity.

Peer Mentoring. In our pilot study, participants requested a peer mentorship program. Peer mentorship offers a way for participants to share their experience with each other. The study team does not monitor these calls. Participation in peer mentorship overcomes any implications for times when recruitment waxes and wanes. Participants in our pilot study commented on how much they liked to help mentor new participants after they complete the program because it helps keep them keep accountable for their own behavior changes and weight maintenance.

Group Support. Skill building sessions at the Clinical Research Center (CRC) Demonstration Kitchen are an important part of the weight maintenance phase of the intervention. Group skill building sessions offer social support. For each of the 4 in-person sessions, participants and their spouse/caregiver(s) interact through cooking demonstrations and hands-on educational sessions. The modules focus on dietary strategies for PCa survivorship with the topics listed in **Table 2**. The group meets every 6 weeks and includes interactive games at

each session to engage attendees. Some examples of these games included the attendees competing to see who can form a meat patty closest to 3 ounces or guess how many sugar cubes are in some of their favorite drinks. The hands-on learning engages sensory concepts with tasting, measuring portions, exercising, and interpreting food labels. Our approach re-emphasizes the nutrition education during the pre-surgical phase, but adds a superior opportunity as the participants transition from meal replacements to a greater reliance on the participants preparing more of their own meals. In addition, the group sessions are lively and fun as the participants, spouses, and our team shares recipes, tactics, and pearls of wisdom. Participants who join by videoconference can view and interact with the group, but they do miss the tastings and hands-on games.

Diet. During weight loss, participants are assigned an energy target which is 500-1000 Calories/day below energy requirements to maintain weight (based on,[54, 63]) and adjusted based on the rate of weight loss (to achieve ≥ 5% weight loss prior to surgery) and self-reported hunger. The target is usually around 1200-1400 Calories/day and the participants see their Calorie targets on the dashboard of the app so they can self-monitor and make decisions based on the amount of Calories remaining each day. Men are taught the basic principles of energy balance and the dieting strategy is simple while the pleasure of eating is maintained. This strategy is consistent with other weight loss programs targeted for men.[55]

The rationale for using meal replacements (MR) in our approach is that MRs lead to greater weight loss in short-term interventions,[64] we need to replace unhealthy snacks with healthy ones,[56] and we need a palatable delivery of soy-based protein to displace red meat intake. Participants will be provided with and asked to consume 5 meal replacements (MR) per day. Medifast Meals® are shipped directly to participants' homes. Each MR from Medifast® provides 90-110 Calories, 10-15 g carbohydrates, 4-5 g fiber, 10-15 g protein, 0-3.5 g fat, and is fortified with at least 20% of the daily value for 24 vitamins and minerals. The MR nutrient information is nearly identical across products, and over 40 products are available to prevent boredom and burnout with more food-like options such as oatmeal, soups, crunchy snacks, and also more typical MR forms like shakes and bars. Participant choices are guided by the health educator so that they consume at least 25 g of soy protein per day to meet the FDA Soy Protein and Heart Disease Health Claim.

Adherence to the American Institute for Cancer Research (AICR) lifestyle recommendations is associated with a 13% reduction in aggressive PCa for each recommendation followed,[65] suggesting that a comprehensive lifestyle change should be emphasized rather than weight management alone. However, a multi-modal approach with too many changes at once can overwhelm people, especially as they are faced with a new cancer diagnosis. Our approach simplifies the adaptation of adhering to multiple AICR guidelines at once by using a meal replacement plan. The development of our novel program was guided by the AICR Second Expert Report,[66] the WCRF Continuous Update Project,[67] and our experience with diet counseling for men with high risk of developing PCa.[68, 69] Commercial programs as part of a comprehensive lifestyle intervention are an option for quicker and more significant weight loss within this treatment paradigm.

The meal plan focuses on weight loss with a diet of less red, processed, or charred meat, more vegetables, and less sugar. All participants will follow the Medifast® 5 & 2 & 2 Meal Plan™ which includes a total of five MR products per day, two Lean & Green™ Meals and two Healthy Snacks. The Lean & Green™ Meals are prepared by the participants and each consists of 5-7

oz. of lean protein (emphasizing white meat, vegetarian protein or seafood), 3 servings of non-starchy vegetables, and up to 2 servings of healthy fat. The 2 healthy snacks consist of fruits, nuts, or whole grains. Participants log their diet in the LST AtHome app which shows the participant where they stand with the Calories/day and food group tallies on the welcome dashboard. Participants receive an encrypted text as a compliance reminder.

Physical activity. In a randomized, controlled, weight loss intervention in men, increases in physical activity mediated the greatest effect on weight loss, accounting for 47% of the intervention's effect on weight loss.[56, 70] In our study, exercise duration and intensity are increased through a home-based program where participants choose their own activities, based on what they find enjoyable and convenient. Home-based programs have been shown to produce greater long-term adherence compared to on-site programs.[71] Exercise recommendations are increased gradually, consistent with national guidelines for weight management.[72] Recommendations are tailored to be more meaningful to men emphasizing how exercise fits into energy balance and adapts easily into their lifestyle (e.g. walking the golf-course, physical labor, etc.). Some participants initially expressed boredom or lack of incentive. Group sessions and peer support helped these participants brainstorm ways to keep engaged by listening to audiobooks while exercising or signing up for run/walks that support charities or causes that resonate with them. Many participants in the pilot study also requested specific exercise instruction for functional or home strength training. Our team created short exercise videos to meet the participants' needs that are customizable with our technology by adding or removing exercises to the participant's app as they are ready. Participants log their intentional exercises in the LST AtHome App, and the overall physical activity goal for each participant is ≥150 minutes of intentional exercise per week.

Wearable Accelerometer: Each intervention participant wears a wrist accelerometer, which is an electromechanical device, used to measure acceleration forces to sense movement or vibrations. The Garmin Vivofit® 3 is a 3-axis MEMS accelerometer from Analog Device; two axes determine most of the two-dimensional movement while the third axis monitors 3D positioning. The sensitivity of these devices is quite high as they are intended to measure very small shifts in acceleration. The accelerometers are distributed to participants as an objective measure of activity and added incentive to engage in physical activity. Although simplistic pedometers could measure steps, the accelerometer offers many advantages. The most important advantage is that participants in our pilot study keep commenting on how motivating they find the accelerometer to compare their steps day to day, view the count down to their daily step goals on the face of the wearable, and see how they compare with other participants on the step leaderboard (via aliases to protect identity). Participants frequently mention how they really want to "earn" their Vivofit® at the end of the study, and so far, everyone has earned one to keep by the points earned through their consistent tracking within the app. The main limitation of the accelerometer is that our team cannot discern sitting from standing. However, the most detrimental aspects of physical activity tracking are participants forgetting to charge, sync, or wear their accelerometer. Our pilot has not had any of these issues because the devices are water proof, have a 30-day memory and the participants considered their devices "very useful". The Garmin Vivofit® 3 syncs seamlessly within the LST AtHome app, thereby reducing any burden associated with tracking. The overall step goal is to progress to ≥10,000 steps/day.

Technology and Tracking. In our pilot study, we collaborated with LifeScience Technologies (LST) Home Care Monitoring System to customize a seamless self-monitoring system for body weight, diet, physical activity, and adverse events specific to our PCa patient preferences. In this customized program, both participants and health educators can input and view data in real-time. The bi-directional communications are encrypted both at rest and in transit, making the

data unreadable, and unusable if the communication is intercepted or accessed without authorization. The system has a patient-facing user platform and a coach-facing monitoring platform.

Patient-facing user platform (LST AtHome). The patient-facing LST AtHome app runs on any device connected to the internet through either an app or web format. The dashboard clearly shows the participants their energy target, their weight progress, a tally of food groups, and physical activity tracking. Each card on the dashboard opens an applet to manage nutrition, physical activity, body weight, or obtain education (exercise videos, preparing/recovering from RP, recipes). The applets presented to the participant are selected by the study team based on the needs of the participant. LST AtHome captures and reports data, and rewards participants for healthy activity through points and leaderboards.

Coach-facing monitoring platform (LST monitor). The health educator-facing LST Monitor shows body weight, diet, physical activity, and adverse events of all the participants at once to the research team in aggregate. The LST Monitor dashboard shows the research team how each participant is progressing and ranks the participants with the least adherent participants listed first to help identify which participants might need extra support and communication.

Control group. Participants in the control group (n = 20) receive the book, "Dr. Walsh's Guide to Surviving Prostate Cancer" by Patrick C. Walsh and Janet Farrar Worthington as well as the American Institute for Cancer Research booklet, "Heal Well, A Cancer Nutrition Guide" at baseline. Our team will collect the same biomarker, anthropometric, QoL, clinical, and diet recall data from the control group at baseline, 1 week prior to surgery, and 6 months post-operation. The only difference in our interaction with these participants will be the absence of any interventional coaching, technology, or meal replacements.

AIM 3: Test the impact of weight management on QoL in PCa survivors.

Urinary, Sexual, and Health-Related QOL Outcomes. The Expanded PCa Index Composite (EPIC)-26 Instrument is validated for the PCa population. The tool assesses five domains (urinary incontinence, urinary irritation/obstruction, bowel, sexual, and vitality). The form includes 26 short questions. Answers are coded on a scale from 0 to 100 and domain scores are assessed. Higher scores for each of the domains represent a better health-related QOL. Missing values for single responses are imputed to the median prior to calculation of the domain scores.

5. **AIM4: To test the impact of weight management on gut microbiome composition at base line, prior to surgery and 6 months after surgery.**

We will study the impact of weight management on gut microbial populations and also the impact of surgery on the same through an unbiased approach where the common 16S rRNA variable regions will be amplified and sequenced by next generation sequencing. The following is the outline of the steps involved in the proposed microbiome study. Microbial DNA will be isolated from the fecal samples using Qiagen kit and will be analyzed for microbial population estimation using next-generation sequencing of the 16S rRNA region. The obtained raw sequences will be demultiplexed, denoised and annotated using QIIME2 software and then functional metagenome will be predicted using PICRUSt software. Statistical analysis will be performed using QIIME2, STAMP and LEfSe software along with relevant R programming packages.

Data Collection:

CRC Visits All participants will go to the University of Kansas Clinical Research Center at baseline, 1 week prior to surgery, and 6 months after surgery for a blood draw (approximately 3 tablespoons of blood/visit) and assessment of vitals, body weight, surveys, and body composition via iDXA. Blood pressure, heart rate, and body temperature will be assessed at each visit. Surveys may also be mailed or emailed to participants in the event when in-person visits cannot take place. The study will provide return envelopes and postage for mailed surveys. Weight will be collected from the scale provided to intervention participants and from personal scales from control participants, if they own a scale.

Main Outcomes.

Sample collection, processing, and analysis. Whole blood and fecal samples will be collected at baseline, 1 week prior to surgery, and 6 months post-operation. Fresh prostate tissue will be collected and flash-frozen from the RP and stored in vapor phase nitrogen. Paraffin-embedded prostate tissue will also be collected from the RP. Since the majority of PCas originate in the peripheral zone, we will obtain samples from 4 quadrants of the prostate peripheral zone in normal/tumor pairs. H&E staining will determine malignant versus benign tissue. Periprostatic adipose tissue will be collected from the RP.

Blood Immune biomarkers. The primary objective of this project is to assess the impact of weight loss before and weight maintenance after PCa surgery on immunosuppressive factors compared to a randomized control. Although our pilot data suggest MDSCs are a logical target for obesity-driven PCa progression, our team is aware of how other immune cells play an interconnected role. We carefully chose biomarkers that fit our hypothesis within the budget constraints, we will analyze MDSCs and their subtypes, Natural Killer (NK) Cells, and regulatory T cells (Tregs). MDSC subpopulations are defined according to published methods[73] of grouping granulocytic (Lin^- $CD11b^+$ $CD33^+$ $CD14^-$ $CD15^+$), monocytic (Lin^- $CD11b^+$ $CD33^+$ $CD14^+$ $CD15^-$), and immature (Lin^- $CD11b^+$ $CD33^+$ $CD14^-$ $CD15^-$). Natural Killer (NK) cells are defined by CD56 and CD16 expression, and regulatory T cells (Tregs) by CD4+, CD25+, FoxP3+ expression in the blood. Please see our recent publication[9] for additional information about our method.

Blood Inflammation biomakers. The CXCL12/CXCR4/CXCR7 inflammatory pathway is centrally involved in tumor progression and recruiting the accumulation of MDSCs to the tumor microenvironment [13] and obesity-driven CCL7 facilitates the spread of cancer. The CXCL12 chemokine plays an important role in angiogenesis, proliferation, and metastasis to bone.[74] Circulating CXCL12 concentrations are higher in PCa patients than those with benign prostatic hyperplasia.[14, 15] Diet-induced obesity increases CXCL12 transcripts in the fat tissue surrounding the prostate gland, and exogenous CXCL12 treatment stimulates migration and invasion of prostate tumor cells.[16] Neutralizing chronic inflammatory conditions decreases MDSC frequencies and immunosuppressive functions.[32] Although we think that CXCL12 signaling has an important role in recruiting the accumulation of MDSCs to the prostate tissue, MDSC generation, expansion, and functions are known to be under the control of several mediators of chronic inflammation.[75] Given this considerable complexity, we plan to measure additional chemokines and cytokines that are known to be involved in the MDSC-tumor interplay or have a documented role in PCa progression. Elevated IL-6 is associated with MDSC frequencies.[75] Inhibition of IL-6 in mice reduces the MDSC infiltration of prostate tumors.[76] Vascular endothelial growth factor (VEGF) increases MDSC expansion,[77] and interferes with the maturation of immune cells.[78] MDSC migration into the tumor also depends on the receptors (C-C versus C-X-C) produced by the tumor site. Obesity-driven

CCL7 facilitates the spread of PCa. In our own lab, we showed a 12-fold decrease in CXCL13 transcripts in tumor obtained from men consuming soy, which is a component of the meal replacements that were used in this study. Lastly, TNFα and MCP-1 are associated

with PCa progression and death[12], so we are also including them in our analyses. Thus, CXCL12, IL-6, VEGF, CCL7, CXCL13, TNFα, and MCP-1 will be analyzed in our lab by MILLIPLEX® MAP chemokine kits #1 and #2 from Millipore (Millipore, Billerica, MA). The human adipokine panel will be used to measure adiponectin, PAI-1, resistin andleptin.

Fecal sample – Microbiome. Dysbiosis or alteration in gut microbial populations were observed in prostate cancer patients. The impact of weight loss and surgery in microbial composition in PCa patients will be identified in this study.

Tissue— Western Blot. CXCR4 is over expressed in PCa. CXCR4 protein expression is greater in the malignant epithelia than the benign epithelia in samples from patients who underwent RP.[79] The localization of the CXCR4 expression also differs. In malignant epithelia, CXCR4 proteins are strongly expressed in cytoplasmic and nuclear compartments, whereas in normal epithelia, CXCR4 protein expression show weak cytoplasmic but strong nuclear staining.[79] It is unknown if intentional weight loss reduces CXCR4 protein expression or alters CXCR4 localization in humans. CXCR4 and CXCL12 protein expressions will be analyzed from the snap frozen prostate tissue cores by Western Blot through fluorescent detection.

Tissue—Immunohistochemistry. CXCR4 protein localization, MDSCs, and Tregs will be assessed in formalin-fixed paraffin-embedded tumor sections using immunohistochemistry. It is unknown if intentional weight loss counteracts obesity-promoted accumulation of these immune cells.

Adipose Tissue – Immunohistochemistry. Antibodies will be used to stain crown like structures and adipocyte diameter will be assessed.

Cardiometabolic biomarkers. Insulin-resistance promotes MDSC accumulation[31] and our pilot showed significant improvement in measures of insulin-sensitivity. Fasting insulin, fasting glucose, C-peptide, CRP and a Lipid Panel will be analyzed in blood samples collected by Quest Diagnostics Laboratories (Lenexa, KS).

Body Weight, Composition (fat vs. lean mass), & Anthropometrics.

Body weight and Anthropometrics. Body weight (without shoes) in all forty participants will be measured on the same scale at baseline and on the day of each CRC visit using a digital scale accurate to ± 0.1 kg. In the event that weight cannot be obtained at the CRC, it will be obtained from the participant scale provided to intervention participants, or control participants' own scales if they have one. Height will be determined using a wall-mounted stadiometer (± 0.1 cm). Two measurements will be taken and averaged; if the two measurements differ by greater than 2.0 cm, a third measure will be taken. Waist circumference will be obtained immediately below the lowest rib and hip circumference will be taken to calculate waist to hip ratio.

Body composition. Body composition will be assessed in all forty participants by dual-energy X-ray absorptiometry (iDXA) at baseline, 1 week prior to surgery, and 6 months post-operation. The radiation dose for a total body scan is 0.004 mSv.[80] Changes will be assessed in fat mass, visceral adipose tissue and muscle mass.

Baseline Measures

Clinical Research Center (CRC) Visits. All forty participants will go to the KU Clinical Research Center at baseline, 1 week prior to surgery, and 6 months post-operation for a

blood draw and assessment of vitals, body weight, surveys, and body composition via iDXA.

NCI Common Terminology Criteria for Adverse Events. This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0.

Clinical Data and Patient Outcomes. Age, gender, smoking history, comorbidities, erectile dysfunction prior to surgery, nerve-sparing (uni- or bi-lateral) and pathological information pertaining to participants' perioperative and postoperative courses will be abstracted from the medical record, verified with the participant at their study visit, and recorded in the study database. Severity of comorbid disease will be graded according to the Charlson Comorbidity Index, the most widely used index in oncology. Prostate specific antigen (PSA) will also be abstracted from the medical record and covered by conventional care.

Intervention Dose and dherence

Monitoring dietary intake. At baseline, 1 week prior to surgery, and 6 months post-operation, two unannounced, random, 24-hour dietary recalls will be obtained on non-consecutive days (one weekday and one weekend day). The dietary recalls will be analyzed with Nutrition Data System for Research (NDSR) in all forty participants. A study dietitian, staffed by Dr. Hamilton-Reeves, will interview the patient by phone. Dietary intake data gathered by interview is governed by a multiple-pass interview approach.[81] Five distinct passes provide multiple opportunities for the participant to recall food intake. The first pass involves obtaining from the participant a listing of all foods and beverages consumed in the previous 24 h. This listing is reviewed with the participant for completeness and correctness (second pass). The interviewer then collects detailed information about each reported food and beverage, including the amount consumed and method of preparation (third pass). In the fourth pass, the interviewer then probes for commonly forgotten foods. Finally, the detailed information is reviewed for completeness and correctness (fifth pass).

Measures of diet compliance. Participants track their diet in the LST AtHome app and return wrappers from the meal replacements as well as any unused products to the study team.

Research staff counts and records the number of meal replacements remaining. Dietary compliance is verified using the two 24-h dietary recalls described above. Tallies for the intake of each food group as well as energy and major nutrients are summarized and reported. Even though this intervention is short-term, an 80% adherence rate is expected because of the multiple food groups tallied. We plan to conduct a subset analysis to look at the 80%, 90% and 100% threshold adherence groups to assess if there is a difference in outcomes.

Table 3: Schedule of Evaluations

		Weight Loss		Weight Maintenance
	Screening & Registration	**Baseline**	**Prior to RP**	**Post-RP**

Duration		At least 4-16 weeks prior to surgery	1 week prior to surgery	26 weeks after surgery
Informed Consent	X			
Anthropometrics				
Body weight & Height		X	X	X
Waist & hip circumferences		X	X	X
iDXA Body Composition		X	X	X
Health-Related QoL				
EPIC-26		X	X	X
Clinical Data & Patient Outcomes				
Medical History & Comorbidities	X	X	X	X
Dietary Intake				
Two 24-hour recalls		X	X	X
Adherence to Intervention			X	X
Adverse Events				
CTCAE 4.0			X	X
Blood & Tissue and Fecal Tests				
Immune Biomarkers		X	X	X
Inflammation Biomarkers		X	X	X
Cardiometabolic Markers		X	X	X
Microbiome		X	X	X

Justification of sample size: We powered this study for aims 1 and 2, but aim 3 and 4 are exploratory. The power calculations used effect sizes and standard deviations from our pilot study (ClinicalTrials.gov: NCT02252484). The primary objective is to reduce obesity-driven biomarkers (MDSCs) of PCa recurrence and death. Our pilot study showed that weight loss of 1.2 pounds/week corresponds to a decrease in MDSC by 1.4 counts/week. Group sample sizes of 17 and 17 achieve over 80% power to detect a change in MDSC of 1.2 per week between the intervention and control groups with standard deviations of 1.6 and 0.3 (obtained from our pilot study) with a significance level of 0.05 using a two-sided, two-sample t-test. Secondary objective: Thirty-four participants will detect weight change as low as 0.5 kg/week between the intervention and control groups using the standard deviations of 0.6 and 0.1, from our pilot study. Weight maintenance will also be examined. If the intervention maintains their weight loss within 3%, 17 patients will give power over 80% to detect equivalency in the intervention group assuming the moderate correlation of 0.4 using paired t-tests. Tertiary objectives to assess the impact of weight loss on QoL using the EPIC-26 tool are exploratory. The results will be used to calculate effect sizes for a definitive, large multi-site clinical trial.

Statistical Analysis Prior to initiating outcome analyses, we will summarize the baseline characteristics of the data. Tests will be considered significant if the *P*-value is less than 0.045 for the final analysis. Our data may include missing observations related to either attrition or nonresponse and this type of missing data can reasonably be assumed to be random. We will run an intention to treat analysis for all outcomes. Comparisons will be carried out separately for the weight loss phase (enrollment to 1 week prior to surgery) and the weight maintenance phase (1 week prior to surgery to 6 months after surgery). Since patients will be on the pre-surgical phase for varying durations of time, we will assess the rate of weight loss between the two groups. A two-sample t-test will be used to assess the differences in outcomes between the two groups. The significance of within-group differences will be assessed using a paired t-test.

Therefore, 34 eligible, randomized patients will provide sufficient power for both aims 1 and 2. However, based on our pilot study, we anticipate that 10% of patients will drop out by the 6 months follow up. Incorporation of this dropout rate inflates the required sample size by a

factor of 34/0.9 = 38 eligible patients. Finally, assuming a 5% ineligibility rate, a total of n = 40 registered patients will be required. A single interim analysis for efficacy will be conducted when 50% of patients achieve their endpoint, at the alpha = 0.005 level. Accordingly, the final analysis will be conducted at the alpha = 0.045 level.

Potential difficulties

- *Tracking/technology.* In our pilot study, many participants were unfamiliar with the technology used and they had never tracked diet or physical activity before. For these participants, we initially offered paper journals so they could track their meal plans by hand. Then, coaches would help them enter the data at the visits. We will offer the same strategy in this project. Also, some participants wanted to remove their accelerometers after surgery because their step counts dropped so low. Our team affirmed that disruptions in sedentary activity (as prompted by the Vivofit® 3) is more important for their health then absolute step counts in the early days after surgery. Coaching participants to reframe negative feelings has helped to overcome this obstacle.

PROTECTION OF HUMAN SUBJECTS

Recruitment Potential subjects will be approached by their urologist or oncologist and informed about the possibility of research participation. Patients who are interested in learning more about participation will be introduced to the study coordinator who will then explain the study in detail. The potential subjects will have the opportunity to read the consent form in the absence of the PI and study team. It will be explained to the subjects that the study is voluntary and that they may discontinue at any time without prejudice.

Informed Consent Informed consent is a continuous process of communication and acknowledgement over time, not just a signed document. The study coordinator will verbally explain the study in detail to participants who are interested in learning about participation in the trial. Then, the potential subjects will have the opportunity to read the entire consent form in the absence of the study team. This process ensures respect for persons through provision of thoughtful consent for voluntary participation. Sufficient time for consideration will be provided in a non-coercive, unhurried environment. Next, the study coordinator will sit with the participant to go over the consent form again, verbally. Information will be presented in a manner that will enable the participant to voluntarily decide whether or not to participate as a research subject. The procedures used in obtaining informed consent will educate the subject population in terms that they can understand. Therefore, the informed consent language and its documentation are written in "lay language" and presented in a way that facilitates understanding. It will be explained to the subjects that the study is voluntary and that they may discontinue at any time without prejudice. Subjects will have the opportunity to ask questions before signing the consent form. Subjects who agree to participate will be consented in a private, closed-door setting. The consent document will be revised when deficiencies are noted or when additional information will improve the consent process. Informed consent will be documented by the use of a written, IRB-approved consent form and signed and dated by the subject or the subject's legally authorized representative. A signed copy will be given to the person signing the form.

Consent forms, and all other study documentation, will be retained in accordance with the KUMC Research Records Retention Policy. This policy states, in part, that research records are to be retained by the investigator for a minimum of seven years.

Risks of participation There is minimal risk to an 8-week delay in surgery. Food diary collections involve inconvenience, but no risk. Blood will be drawn by a trained phlebotomist or nurse and could result in a small bruise, a minor risk. Unusual changes during or following an exercise session may occur. These may include muscular or joint injury, abnormal blood pressure, fainting, disorders of heart beat, and/or very rare instances of heart attack or death. Subjects will be exposed to radiation in this study from 3 total body iDXA scans. The risk from this radiation exposure is very low. Subjects may be embarrassed or feel uncomfortable by some of the questions in the surveys. Subjects are free not to answer any questions. It is possible that confidentiality of the group sessions would not be maintained as other subjects may disclose information heard during a meeting There may be other risks of the study that are not yet known.

Another risk to participants is the breach of confidentiality and loss of privacy from disclosure of their protected health information. Limited participant information will be shared with representatives of Quest Diagnostics, LifeScience Technologies, Inc., Medifast®, Garmin International, Inc., Carematix, and Zoom Video Communications, Inc. These groups will only have access to the participant information that is critical to their part of the intervention or analyses to make sure the study is done properly. However, this study presents minimal risks to the participants whose data are being analyzed because we will take rigorous precautions to protect privacy, confidentiality, and security of personal health information, as described below.

Protection against risk All participants will be followed and managed by their surgeon according to standard guidelines. Any interventions, including Dual Energy X-Ray Absorptiometry (iDXA) will be performed at the discretion of the surgeon. All personnel will complete training for ethical research and human subjects' privacy and protection.

Data Management

Access to study data is protected and subject to the same security protections as other confidential health system data; computer passwords are changed on a regular basis. Individual identifiers such as names and medical record numbers will be removed from study data files in the data processing steps. Unique study-specific identifiers will be assigned to support accurate linkage of data on the same individual across timeframes and across data files. Any protected health information (PHI) data collected are stored under an additional layer of security in the REDCap database and access is severely restricted. With the exception of patient initials and dates, the study team will not release PHI, except as required by law. Only persons directly involved with the study will have access to data identifying individuals. Records and forms will be kept in locked file cabinets when not in use. Names will not be stored on computer files for data analysis. No individual will be identified in the study's results. Data will be managed in the REDCap database running from a HIPPA-certified server that is managed by KUMC Information Security.

Data Management and Security with LifeScience Technologies (LST), Inc

LST systems administrators will have access to data stored in servers via the app. The data collected by the LST app is housed in Microsoft Azure, one of the nation's largest HITRUST certified hosting providers. Back end databases are geographically replicated between two U.S. Azure data centers, while providing a built-in, 30-day, point-in-time recovery.

Permissions for the LST app to access to Location, Calendar, Picture folder, Microphone and HealthKit are prompted through push notifications, and require the participants permission in

order to access. The study team will help guide participants through those permissions. LST pulls data from Garmin by the Garmin user name.

Databases are backed up weekly and websites and virtual machines are backed up daily. Data encryption at rest use AES256 bit encryption and data in transit use HTTPS. LST also exports SQL Server database backups nightly, with AES encryption, to a separate server. This is scheduled as full backups on the weekend, and nightly differentials. Transactional logs are exported hourly. All communication between the device and web servers are conducted over a HTTPS-encrypted connection. All transactions require authentication to complete ensuring only authorized users may access the system. Data stored in Microsoft Azure servers will be destroyed once no longer needed. Software settings will provide de-identification for stored data so that only users with a need will be given access to see identifying information, such as patient names. Subjects who have difficulty or questions about use of the LST app will contact the study team; our LST contact is the second level of support and will provide assistance to the study team as needed, maintaining patient confidentiality. Deactivation of the app is the responsibility of the study team. Once the study is complete, and data collection is no longer necessary the study team will deactivate the app.

Biospecimens
Biologic materials are only obtained after appropriate informed consent of the patient. This informed consent will include appropriate elements required by the National Cancer Institute. Patient specimens are to be stored in a manner in which direct patient identification is not possible. Specimens will be stored without any direct patient identifiers and only identified by patient number. Personnel handling the specimens will be adequately educated about and agree to the confidential handling of specimens. Specimens will be stored in a secure limited access area with backup power for the freezer and an alarm to notify study staff if the freezer falls out of range. Access to the laboratory and clinical outcomes data will be restricted to the study team and statistician. Only select personnel will have the ability to match the identification number with clinical endpoints.

Participation in the study is voluntary and participants may withdraw at any time.

Potential benefits of the proposed research. Prostate cancer is the most common cancer in US men along with the increasing trend toward obesity in the general population. The development of dietary approach to improve outcomes from the surgical treatment of prostate cancer and to better understand how weight control impacts the immune system and inflammatory state will improve the quality of life for cancer survivors. The approach will meet the pressing need to identify weight control interventions for cancer survivors that may improve long-term prognosis and survival. Given the minimal risk to subjects and the potential gain from the study, the risks are considered reasonable.

Adverse event reporting:
Participants will be instructed to report any new or worsening medical condition to their coach or on their weekly self-monitoring logs. Adverse events may be obtained from medical updates taken at baseline, 1 week prior to RP, and 6 months after PCa surgery, weekly participant logs, or spontaneous reports from any source. For all adverse events, an Adverse Event Record Form will be completed that includes a description of the event, a classification of the seriousness, an evaluation of the potential relationship to the intervention, and an assessment of need for change in the informed consent or study activities. Adverse events will be reviewed weekly by the PI and monthly by the study team. Any serious adverse event (SAE) will be investigated immediately and assessed for relevance to the study by the study physicians and

medical monitor. All related and unexpected SAEs will be reported to the KUMC IRB/HSC within 48 hours of the report of the SAE.

Safety Monitoring/Medical Monitor. Serious side effects or other problems during this study will be reported to PI, Dr. Jill Hamilton-Reeves, Co-I, Dr. Brantley Thrasher, and Medical Monitor, Dr. Eugene Lee, MD.

Medical Monitor: *Dr. Eugene Lee, MD*
Assistant Professor of Urology
elee@kumc.edu

An external Medical Monitor will evaluate adverse effects. Dr. Lee is a qualified physician, not associated with this particular protocol and not under the supervision of anyone on the research team. Dr. Lee will monitor data collection and safety by reviewing the research protocol with emphasis on data integrity and patient safety issues. Dr. Lee will monitor any adverse events during the course of the study, make decisions about the continuance of subjects, communicate with the investigators and physicians about adverse events, and assess the responsiveness of corrective actions.

More specifically, the medical monitor will be responsible for reviewing:

- Interim side effect/toxicity data for this trial and proposing corrective actions when the side effects for any treatment are unexpectedly severe. Nonetheless, the PI and study team have primary responsibility for monitoring toxicity. Corrective actions by the medical monitor may include:
    - modifying the treatment
    - early suspension of the trial
    - limiting the participation in the trial to a subset of theoriginal subjectpopulation

- Interim analyses of outcome data prepared by the statisticians, with recommendations for change in the study status on the basis of these analyses. These changes may include:
    - early termination of accrual
    - release of results consistent with any sequential stopping rules used in the design of the study
    - increases to the accrualgoal
    - major changes to the eligibility criteria for the trial

- The impact of independent scientific investigations (other trials) on the trial being monitored, as well as recommending changes based on those external results.

- Requests for data from sponsoring organizations or any other party. This includes requests for preliminary data for planning ancillary studies. These responsibilities end after the unblinding of the trial, with the medical monitor not involved in further review of the trial. However, the research team may consult the medical monitor on other issues thereafter, such as appropriate action for late toxicities.

The medical monitor will have face-to-face meetings with the research team twice per year. More frequent phone conferences will be held if deemed necessary, for an evaluation of adverse events.

ClinicalTrials.gov
The trial is registered on the ClinicalTrials.gov website. ClinicalTrials.gov Identifier:

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