Protocol Title: USE OF ß-HYDROXY-ß-METHYLBUTYRATE (HMB) TO COUNTERACT LOSS OF MUSCLE MASS AND STRENGTH IN OLDER MEN WITH PROSTATE CANCER STARTED ON ANDROGEN DEPRIVATION THERAPY (ADT)

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ADDENDUM 1: Research Protocol

Medical College of Wisconsin

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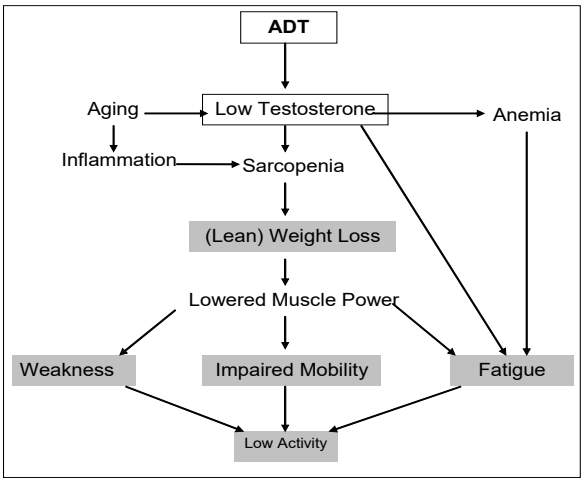
1. INTRODUCTION

Prostate cancer (PCa) is the second most common cancer in men, primarily affecting older men. The standard treatment for recurrent and metastatic Pca is ADT. It is also standard of care for men with intermediate or high risk localized prostate cancer who plan to get radiation to receive ADT in the neoadjuvant and adjuvant setting. It is well established that ADT causes muscle weakness and wasting, osteoporosis, and fatigue. Our preliminary data suggests that older men on ADT have significant physical performance deficits, functional impairments, and falls at higher rates than men in the general geriatrics population. HMB is a leucine metabolite which has been shown to decrease the rate of muscle protein breakdown. When given with arginine and lysine or glutamine, HMB has been shown to improve strength, fat-free mass and function in the general geriatrics population who are prone to sarcopenia. Use of HMB and/or amino acid supplementation in older men with PCa starting on ADT has not been reported. We will prospectively: 1) measure the change in body composition, strength, physical performance, and falls in older men with PCa starting on ADT, comparing those who receive HMB + AG versus those who do not, 2) evaluate the use of MRI and muscle biopsy to identify changes in muscle composition and muscle fatiguability that are known to occur in this patient population. We will test the hypothesis that HMB + AG can reduce the adverse change in body composition and strength/muscle fatiguability that occur when older men with Pca are started on ADT. With data obtained in this study, a larger randomized study will be designed to compare interventions aimed at minimizing the adverse affects that occur with ADT initiation.

Figure 1. Possible Contribution of ADT to the Development of Frailty



2. BACKGROUND

Seventy-five percent of Pca incidence and greater than 90% of Pca mortality occurs in men aged 65 years or older.[1] PCa is the second most common cancer in American men, with more than 217,000 new cases anticipated in 2010.[2] Men live with Pca for many years. Once patients develop biochemical recurrence (PSA rise) after prostatectomy for local disease, the median time to development of distant metastasis *in the absence of treatment* is 8 years and median time to death an additional 5 years after development of metastases.[3] Due to competing comorbidities, a significant number of older men with PCa will die with, ***not as a result of***, their disease. In fact, only 39% of men diagnosed with PCa after age 67 die of their disease.[4] Thus, it is extremely important for providers to be aware of potential toxicities of therapy, as men will likely live with these side effects for many years.

The standard therapy for metastatic and recurrent Pca is ADT, a potentially toxic therapy. It is well established that ADT can cause significant morbidity, including fatigue, anemia, osteopenia/osteoporosis and decrease in muscle mass, occurring ***as early as 1-3 months*** after ADT initiation.[5-8] Patients on ADT for one year have a lower relative muscle mass, reduced upper limb strength, and worse self-reported physical function than those not on ADT.[9] Increased prevalence of fractures in Pca patients on ADT has also been reported, with a positive correlation between number of LHRH agonist doses and fracture risk.[10] Because older men are a "compromised host" who are already experiencing increased comorbidities, limited life expectancy and loss of muscle mass resulting in impaired muscle function associated with aging, they are particularly vulnerable to the potential side effects of therapy. In fact, several of the known toxicities of ADT, including sarcopenia, weakness, mobility problems, and fatigue, are part of the classic components of frailty - a geriatrics syndrome which imparts significant risk for adverse outcomes including falls, disability, hospitalization, and death.[5,11-14] We have hypothesized that ADT may, indeed, ***induce*** frailty in a subset of older men with Pca (Figure 1).[15,16] Despite the known toxicities and lack of survival benefit in many cases, the ***use of ADT has increased by 27%*** in less than a decade.[17]

It is well established that older patients experience age-related loss of muscle mass and function (sarcopenia), presumably due to an imbalance of protein synthesis versus protein breakdown.[18,19] In addition, studies have shown that men who start on ADT experience increased muscle protein breakdown and decreased synthesis.[20] β-hydroxy-β-methylbutyrate (HMB), a leucine metabolite, has been shown to slow protein breakdown. When HMB is given with arginine and lysine (which support protein synthesis) in randomized trials, researchers have shown that elderly men and women who receive this nutritional supplementation experience improvement in fat-free mass, strength, functionality and protein synthesis when compared with controls.[21,22] In addition, patients with advanced cancer who experienced weight loss of at least 5% have also been shown to benefit from HMB, with supplementation resulting in a significant increase of fat-free mass when compared to controls.[23] Thus, it seems reasonable that older men with Pca starting on ADT who experience lean muscle loss as a result of aging and ADT, may achieve some benefit from supplementation with HMB as well.

Strength can be defined as the maximal voluntary force generating capacity of a muscle or muscle group (i.e., MVC). Muscle strength is directly related to muscle mass, and in turn, to muscle contractile or fat-free cross-sectional area (CSA). Muscle CSA in older adults can be measured accurately and non-invasively by magnetic resonance imaging (MRI) techniques and much of what we know about sarcopenia comes from such studies.[24,25] Specific strength is the ratio of MVC/CSA. A loss of muscle mass, such as from sarcopenia, can lead to weakness without a change in specific strength. A decrease in specific strength would be indicative of central activation failure or a change in the intrinsic ability of the muscle to contract (i.e., altered intramuscular proteins).

Muscle fatigue can be described as a decrease in the force generating capacity of muscle or as a decreased time to task failure or endurance time.[26] Muscle fatigue has been extensively investigated in older adults and in PCa survivors undergoing radiotherapy using standard electrophysiological techniques.[27] Muscle oxidative capacity, an index of muscle fatiguability, can be indicated by the 31P-MRS during conscious exercise in humans and has been used to successfully study muscle fatigue in chronic disease .[28]

Muscle biopsies can be used to better understand the pathophysiology behind muscle loss. There are two types of muscle fibers: fast and slow. Slow muscle fibers are important for postural standing, while fast muscle fibers are important for quick movements such as catching oneself while tripping.[29] Both are important in older patients prone to falls.[29] Muscle biopsies have been done in healthy subjects; the procedure is minimally invasive and well-tolerated.[30]

We propose to study to use of HMB plus amino acids in older men with Pca starting ADT. We hypothesize that the use of this nutritional supplementation will decrease the loss of muscle mass and strength that occurs when men start ADT. Use of HMB in men with prostate cancer has not been reported, thus this is a completely novel study. The strength of this project lies in the multidisciplinary approach to evaluation of muscle loss and strength in this patient population. We plan to use geriatric functional assessments, MRI measurements and pathologic evaluation of muscle. We have incorporated a very diverse team including medical oncology, geriatrics, radiology, pathology and exercise physiology, with each member of the team adding their extensive expertise in their given area. For this reason, we feel that this is a very strong proposal which will fundamentally address a promising approach to this important clinical problem.

Preliminary data:

Abnormal physical performance and frailty in older men on ADT (Bylow). In a cross-sectional study of 50 older men (age ≥70) with Pca on long-standing ADT, we found that these men are markedly disabled.[31] 50% had abnormal scores on the Vulnerable Elders Score, a geriatric screening tool that identifies patients at risk for functional decline. 24% had impairments in Activities of Daily Living (ADLs); 42% had impairments in Instrumental Activities of Daily Living (IADLs); 50% had abnormal physical performance measures, and 22% reported a fall in the last 3 months. All of these exceed percentages for age- and gender-matched populations.

Table 1. Case-control study comparing frailty/disability for older men on ADT for 6+ months vs. controls off ADT.			
	Mean ± SD or %		p-value
	ADT (N = 63)	Controls (N = 71)	
Age	72.1± 7.0	70.5 ± 6.3	0.21
Body Mass Index			
Underweight (< 18)	0.0	0.0	0.04
Normal (18.5-25)	13.5	20.6	
Overweight (25-30)	40.4	58.8	
Obese I & II (30-40)	40.4	19.1	
Severely obese (40-45)	5.8	1.5	
Modified Fried's Frailty, Score (0-5)			
0 "Robust"	34.8	48.5	0.02
1 "Prefrail"	32.6	38.5	
2 "Prefrail"	23.9	10.3	
3+ "Frail"	8.7	2.9	
Fall within past 6 months	14.3	2.8	0.02
Osteoporosis	14.3	4.2	0.04
Testosterone (ng/mL)	21.2 ± 30.9	377.9 ± 146.9	< 0.01

A second cross-sectional pilot study (Table 1) was performed which compares older men with biochemical recurrence of PCa on ADT to controls, defined as men with a history of Pca who are status post definitive local therapy with no evidence of disease recurrence.[16] In this study, funded by an American Society of Clinical Oncology Young Investigator Award (Bylow), we evaluated frailty, physical performance and falls in both groups. Our hypothesis was that those men on ADT would have a higher prevalence of frailty, abnormal physical performance and falls than controls. When using a modified version of Fried's frailty index,[32] substituting obesity (resulting in lean body mass loss) for weight loss, we found that men on ADT were significantly more frail (Table 1). In addition, men on ADT were significantly more likely to report falling in the last six months, possibly due to the muscle loss and weakness they experience on ADT.

Prostate Cancer-Related Fatigue (CRF) and Radiation Therapy (Ng).[27,33,34] 12 Pca and 12 healthy control subjects participated. The cancer survivors were tested before and after 6 wks of external beam radiotherapy. The control group was tested at similar times with no intervention. MVC or strength, muscle endurance, muscle oxidative capacity were measured from the ankle dorsiflexor muscles. Oxidative capacity was measured using 31P-MRS. Prior to therapy, both groups were similar in MVC, endurance, sleepiness, and depression. Following radiation therapy, muscle endurance decreased in the cancer group (pre, 556 ± 98s, post, 391 ± 51s, mean ± SE, p=0.001), with no change in strength. In contrast, endurance time in the control group increased (pre, 616 ± 112s post, 753 ±160s, p=0.03) after 6 wks, also with no change in strength. Preliminary MRS results are consistent with decreased muscle oxidative capacity. These unique studies also demonstrate the feasibility of using magnetic resonance and physiological techniques to assess muscle function in men with Pca. Unlike radiotherapy, we expect significant changes in muscle strength and composition with ADT.

3. HYPOTHESIS AND OBJECTIVES

Use of HMB and/or amino acid supplementation in older men with PCa starting on ADT has not been reported. We will prospectively: 1) measure the change in body composition, strength, physical performance, and falls in older men with PCa starting on ADT, comparing those who receive HMB + AG versus those who do not, 2) evaluate the use of MRI and muscle biopsy to identify changes in muscle composition and muscle fatiguability that are known to occur in this patient population. We will test the hypothesis that **HMB + AG can reduce the adverse change in body composition and strength/muscle fatiguability that occur when older men with Pca are started on ADT.** With data obtained in this study, a larger randomized study will be designed to

compare interventions aimed at minimizing the adverse affects that occur with ADT initiation.

Objectives:

1. Prospectively measure the change in body composition, strength, physical performance measures, and falls in older men with PCa starting on ADT, comparing those who receive HMB + AG versus those who do not.
   Hypothesis: Men who are randomized to receive HMB + AG will experience less lean body mass loss, less decrease in strength, less decline in physical performance, and fewer falls than those who do not receive HMB + AG.

2. Prospectively measure the fatiguability and muscle size using MRI/Phosphorus MRI spectroscopy (^{31}P-MRS) in older men with PCa starting on ADT, comparing those who receive HMB + AG versus those who do not.
   Hypothesis: Men who are randomized to receive HMB + AG will experience less muscle fatigue and less loss of muscle cross-sectional area than those who do not receive HMB + AG.

3. Prospectively analyze muscle fiber cross sectional area and fiber type using muscle biopsy in a subset of men with PCa starting ADT, comparing those who receive HMB + AG versus those who do not.
   Hypothesis: Men who are randomized to receive HMB+ AG will experience less loss of cross-sectional area and less loss of fast type II fibers than those who do not receive HMB + AG.

4. SELECTION OF PATIENTS

Prostate cancer patients under the care of an MCW Cancer Center physician will be eligible to participate.

Inclusion criteria:

1) Histologically confirmed adenocarcinoma of the prostate

2) Age 60 years or older

3) Patients with asymptomatic or minimally symptomatic PCa for which they are about to start androgen deprivation therapy (ADT) per provider recommendation
   - Asymptomatic or minimally symptomatic (as judged by treating physician) metastases allowed
   - Men receiving ADT for localized prostate cancer are allowed

4) Patient able to give informed consent.

Exclusion criteria:

1) Patient already on ADT

2) Patients who are visiting clinic for a second opinion only

3) Patients with a diagnosis of dementia

4) Patients with a diagnosis of a neuromuscular disorder (i.e. multiple sclerosis)

5. STUDY DESIGN AND STATISTICAL CONSIDERATIONS

Objective 1: *Prospectively measure the change in body composition, strength, physical performance measures, and falls in older men with PCa starting on ADT, comparing those who receive HMB + AG versus those who do not.*

Rationale: Older men with prostate cancer who start on ADT experience clinically significant muscle loss and weakness as a result of treatment, likely contributing to increase risk of falls and fractures and decreased quality of life. Treatments are needed which counteract the loss of muscle mass and strength caused by ADT. HMB + AG, which decreases protein/muscle breakdown, has been shown to increase lean muscle mass and strength in elderly men and women. It seems plausible that HMB + AG could counteract the muscle loss and weakness that men experience as a result of ADT; effectiveness of HMB + AG in men with prostate cancer starting ADT has not been studied.

Experimental Design: We will conduct a prospective cohort pilot study of men age 60 and older with Pca who are about to start ADT. All men will be followed prospectively for 3 months from time of initiation of ADT. Men will be randomized to receive HMB + AG versus no supplement (Figure 2). Assessments will be performed at baseline (before or within 2 weeks of starting ADT) and 3 months (Table 2). Adherence to HMB will be assessed by patient diaries. Functional assessments and basic strength measurements will be performed at baseline and 3 months. These will include the Short Physical Performance Battery (SPPB), a validated measure which evaluates balance, gait, strength, and endurance and has been shown to predictive of morbidity and mortality at 4 years.[35,36] Hand dynamometer (grip strength, predictive of morbidity and mortality on older patients) and 3 month history of falls will also be assessed. Physical activity will be measured with tri-axial accelerometers (Actigraph, Pensacola FL) that persons will wear on a belt around the waist for 7-days.[37] This has been used previously in men with prostate cancer.[27] Body composition will be measured with Dual-emission X-ray absorptiometry (DXA) scan at baseline and 3 months. Muscle strength will be measured with non-magnetic force transducers and composition will be measured with MRI at baseline and 3 months (SA2). Muscle biopsies will be done on a subset of patients who agree to the procedure (SA3).

Setting: The patients will be recruited from Oncology and Urology clinics at Froedtert Hospital. PCa patients in the clinics who consent to participate in this study will do physical performance testing at each assessment. A trained research assistant (RA) will administer testing and enter data into a secure database. Serious adverse events and study progress for this investigator initiated trial will be monitored by Kathryn Bylow, MD per NCI CCSG guidelines. Recruitment: Based on the number of patients currently seen in these clinics, approximately 2-3 patients will be seen a week who are eligible for this study. A total of 80 patients (40 in each arm) will be enrolled in this pilot study.

Figure 2. Trial design

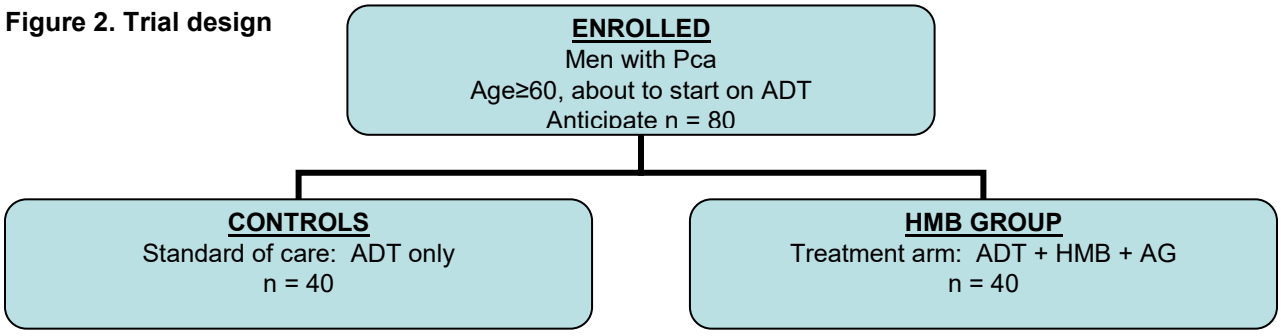


Table 2: Measures performed over time per group						
	Baseline			**3 months**		
	SPPB HD falls	MRI	Biopsy	SPPB HD falls	MRI	Biopsy
Control	X	X*	X*	X	X*	X*
HMB	X	X*	X*	X	X*	X*
SPPB: Short Physical Performance Battery; HD: hand dynamometer; * MRI and Biopsy to be done on subset of sample						

Data Analysis:

Study design: The trial will be conducted in two phases, with 40 patients recruited for both phases. After the first 40 patients have been evaluated, a two-sample one-sided t-test comparing the mean lean body mass loss will be conducted. If the one-sided p-value is equal or less than 0.0088, the trial will be stopped for efficacy. If the p-value exceeds 0.3, the trial will be stopped for futility. In all other cases the trial will proceed to the next phase. At the end of the second phase a two-sample one-sided t-test comparing the mean lean body mass loss in the two groups will be conducted at a 5% significance level. **Randomization**: Randomization will be stratified by exercise status to ensure almost equal representation of both strata in both treatment groups. A block-size of 8 will be used, that is among each 8 consecutive patients exactly 4 will receive each treatment. Due to the presence of strata this blocking will not ensure exactly equal group size, however compared to un-blocked randomization it will keep the group-size difference lower. **Sample size considerations**: The study was powered to detect a smaller lean body mass loss by 0.8 kg in the treated group using a one-sided two-sample t-test at a 5% significance level. This effect size corresponds to approximately 50% of the expected lean body mass loss in the control group, and is similar to the effect achieved by an exercise intervention.[38] Based on literature review the standard deviation of within-person lean body mass change was assumed to be 1.4kg.[38,39] The following table shows the power of the study and the probability of early stopping for efficacy/futility with the planned total sample size of 40 subjects per group and one interim analysis after 20 patients. The values are based on 10,000 simulation runs.

Difference in lean body mass loss, kg	Probability of early stopping for efficacy	Probability of early stopping for futility	Overall power
0	0.9%	70.3%	4.7%
0.4	6.5%	35.4%	33.7%
0.8	26.4%	10%	78.0%
1.2	59.5%	1.5%	97.5%
1.6	86.8%	0.1%	99.8%

Statistical analysis plan: As described in the study design, the primary outcome of within-person lean body mass change will be analyzed using a one-sided two-sample t-test. This test will be conducted at a 0.88% significance level after 20 patients have been evaluated in both arms, and, if the study proceeds to the end, at a 5% significance level after 40 patients have been evaluated in both arms. The secondary outcomes will be evaluated using a t-test or Wilcoxon rank-sum test as appropriate.

Anticipated Results/Interpretation: We anticipate that body composition will be better preserved in the supplemented group after initiation of ADT. In addition, we expect less functional limitations to mobility in the supplemented group as indicated by greater physical activity as measured by accelerometry. Further we expect physical activity to be positively related to muscle strength and endurance.

Objective 2: *Prospectively measure the fatiguability and muscle size using MRI/Phosphorus MRI spectroscopy (^{31}P-MRS) in older men with PCa starting on ADT, comparing those who receive HMB + AG versus those who do not.*

Rationale: Fatigue is highly prevalent in men with PCa undergoing ADT and can affect QOL. Muscle fatigue could be due decreased oxidative capacity as a primary or secondary effect of the cancer or its treatment. Fatigue could also result from muscle weakness or loss of strength. The later could occur when a smaller amount of muscle has to accomplish the same amount of work as that of a larger amount. 31P- MRS is a non invasive *in vivo* technique which can be used to study phosphorus energy metabolites in conscious humans during exercise. As such, it can help to delineate the causes of muscle fatigue in PCa with ADT. We expect both to play a role. HMB + AG has been shown to increase muscle strength in older patients. It stands to reason that muscle strength and fatiguability would improve in older men with prostate cancer on ADT who receive HMB + AG.

Experimental Design: A subset of consenting patients (estimated 20 per group) will be assessed at time increments as outlined above. Cross sectional area of quadriceps muscle will be assessed using MRI. Muscle fatiguability will be measured as time to task failure (i.e. endurance and PCr recovery) using 31P-MRS at baseline and 3 months.

Data Anlaysis: Exploratory MRI studies will be conducted on the first 40 consenting patients. This sample size will provide an 80% power to detect large effects with effect size of 0.9 or above at a two-sided 5% significance level.

Anticipated Results/Interpretation: We expect lean cross sectional area and therefore strength to be preserved or enhance in the HMG+AG group. We also expect endurance and muscle oxidative capacity to be preserved or enhanced in the HMG+AG group.

Objective 3: *Prospectively analyze muscle fiber cross sectional area and fiber type using muscle biopsy in a subset of men with PCa starting ADT, comparing those who receive HMB + AG versus those who do not.*

Rationale: Studies in older patients indicate that HMB, when given with amino acids, helps to maintain protein synthesis and slow muscle breakdown. ADT is known to cause accelerated loss of lean muscle mass. HMB + AG, when given to men starting androgen deprivation therapy, may prevent loss of lean muscle mass. Biopsy of muscle will definitively show cross sectional area and fiber type (fast versus slow) in this patient population. A better understanding of changes in fiber type will clarify the pathophysiology behind ADT toxicity and the potential mechanism of action of HMB + AG.

Experimental Design: A subset of patients will undergo muscle biopsy (vastus lateralis) at baseline and 3 months. We will compare pre-ADT versus post-ADT muscle biopsy for fiber type composition and fiber type cross sectional area. Muscle fiber type histochemical staining will be done as follows: 1) Biopsies will be quick frozen in isopentane cooled with liquid nitrogen, 2) Store frozen pre sample at -80C until get individual's post sample, 3) Cut 10 micron cross sections of pre and post and collect sections on same slide; process together in same incubation medium to prevent variation in day to day composition of the incubation conditions, 4) Incubate slides for histochemical myofibrillar ATPase activity using acid-preincubation and alkaline-preincubation to accentuate fast and slow fiber subtypes,[40] 5) Based on muscle fiber staining intensities, quantified with MetaMorph computerized optical density readings, segregate fibers into fast and slow fiber types and determine the percentages of each type. For each fiber, measure its cross sectional area using MetaMorph digitizing planimetry. A separate consent form will be provided to consent for this procedure. We will compare those who receive HMB + AG to those who do not.

Data Analysis: Exploratory muscle biopsies will be conducted on the first 10 consenting patients. This sample size will provide an 80% power to detect large effects with effect size of 0.9 or above at a two-sided 5% significance level.

Anticipated Results/Interpretation: The percentage of fast fibers will decrease post ADT. Slow fibers will transform from slow to fast (shift in gene expression from slow myosin to fast myosin). The cross sectional areas of fast and slow fibers will decrease post ADT. ADT causes decreased synthesis of contractile proteins so muscle fibers atrophy. The post ADT shift in slow to fast fibers and fiber atrophy will cause the individual to

exhibit greater muscle fatigue and weakness. The fast fibers are more fatigable than slow fibers. Slow fibers are normally utilized to maintain posture, against gravity. They can contract for long periods without fatiguing. Fast fibers are fatigable so the person is likely to have difficulty maintaining posture. The reduced cross sectional areas of both fiber types represent a decrease in contractile proteins and less force output of the muscle. The individual is more likely to fall. HMB + AG treatment will prevent the post ADT shift from slow to fast fiber transformation and prevent muscle fiber atrophy. HMB individuals will have less fatiguability, stronger and less likely to fall.

6. RISKS TO PATIENTS

HMB + AG: Based on prior studies, those patients who receive HMB+AG vs placebo may have a higher incidence of dry scalp and heartburn. No other significant adverse reactions have been reported.

Functional assessments: Functional assessments are quite simple and have been shown to be very safe in geriatric patient population. It is possible that patient could trip during balance/walking test and injure themselves, although risk is very small.

Imaging: It is possible that patients may experience some anxiety as a result of imaging, although chance of this is minimal. Patient may experience mild discomfort as a result of lying flat for a period of time on hard surface for both DXA scan and MRI. As we are just imaging lower extremity, patient's head will be able to remain outside of tube for MRI so claustrophobia should not be an issue.

Muscle Biopsy: Patients may experience some pain due to muscle biospsy. There is also a small chance of bleeding or infection related to this procedure. Patients are not required to participate in this portion of the study.

Confidentiality risks: Though we will make every effort to maintain participant confidentiality, the loss of confidentiality is a risk.

Patient Costs: There will be no additional cost to the patient, as the cost of ^{31}P-MRS, DXA scan, functional assessments and immunohistochemical stains will be covered by a MCW Cancer Center grant. The patient and/or their insurance carrier will be responsible for all charges relating to standard of care labs, doctor visits, and imaging deemed necessary by patient's provider to assess status of prostate cancer.

7. ADVERSE EVENT REPORTING REQUIREMENTS

Any adverse events will be reported based on the NCI Common Toxicity Criteria (CTC) version 3.0. SAE's that occur will be reported to the IRB following the IRB Reporting Guidelines. Adverse events (AE's) or Significant adverse events (SAE's) will be collected until 30 days after the completion of study (4 months from enrollment).

8. DATA SAFETY MONITORING COMMITTEE (DSMC) REPORTING

This study will be reviewed by the Medical College of Wisconsin Cancer Center Data Safety Monitoring Committee (MCW CC DSMC). A summary of the MCW CC DSMC activities are as follows:

- Review the clinical trial for data integrity and safety
- Review all unexpected grade 3, and all grade 4, and 5 adverse events, as well as any others requiring expedited reporting as defined in this protocol. (Grades 4 & 5 events must be reported to the DSMC within 5 calendar days of study staff's knowledge.) Review all DSM reports
- Submit a summary of any recommendations related to study conduct
- Terminate the study if deemed unsafe for patients

A copy of the MCW CC Data and Safety Monitoring Plan and membership roster will be maintained in the study research file and updated as membership changes. The committee will review reports from the study PI twice annually (or more frequently if needed) and provide recommendations on trial continuation, suspension or termination as necessary.

Any available DSMC letters will be submitted to the IRB of record as required.

9. STORAGE OF RESEARCH SPECIMENS

Muscle biopsies will be stored until follow up biopsy completed 3 months later for each patient. Details of this process outlined in Objective 3 above. These biopsies will be de-identified by Dr. Riley, and a private patient identification number will be used on these slides. The key for this identification system will reside on Dr. Riley's password protected computer. Those de-identified specimens will be stored in the lab of Dr. Riley. The prepared slides from the biopsies and the protected health information (PHI) may be stored up to 10 years after the end of the study.

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