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TITLE: PROlonged Nightly FASTing for Obesity Reduction and Prevention of Disease in Precursor Multiple Myeloma (PROFAST)

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1. OBJECTIVES

1.1 Study Design

We will conduct a 4-month randomized trial of a prolonged nightly fasting intervention (PROFAST) in 40 overweight and obese individuals with monoclonal gammopathy of undetermined significance (MGUS), smoldering multiple myeloma (SMM), and smoldering waldenstrom macroglobulinemia (SWM). We focus on these individuals because they have multiple risk factors for MM but lack evidence-based strategies to prevent progression to overt malignancy. The goal of the study is to acquire preliminary outcome data suggesting the efficacy of a prolonged nightly fasting intervention on "white" adipose tissue and clinical signs of disease progression in MGUS and SMM patients; we will also explore the degree to which the intervention impacts adiposity in the bone marrow niche. Measurements of these outcomes will be collected at baseline and 4-months.

The intervention is designed to promote a 14-hour fast during the nighttime hours. The intervention will draw from established behavioral change theories, and the mode of delivery will be through telephone counseling and a simple text messaging system.

1.2 Primary Objectives

To investigate the effects of the PROFAST intervention on DXA-derived body composition from baseline to 4-months in patients with MGUS and SMM/SWM.

1.3 Secondary Objectives

- Identify changes in m-protein/light chains between patients randomized to the PROFAST intervention vs placebo.
- Identify changes in hemoglobin concentrations among patients randomized to PROFAST vs. placebo.
- To examine the effects of the PROFAST intervention on bone marrow adiposity
- To explore the degree to which the PROFAST intervention changes metabolites and metabolomic signatures.
- To examine the impact of the PROFAST intervention on changes in quality-of-life indicators form baseline to 4-months

2. BACKGROUND

2.1 Myeloma (MM) and its Precursor Conditions.

The incidence rate of MM in the US is progressively rising; few cancers demonstrate a greater increase in new cases since 2004 [1]. Novel therapies have improved the estimated life expectancy of MM patients, from a 5 year survival rate of 34.5% in 2000 to just over 50% today [1]. However, most patients eventually stop responding to anti-myeloma therapies and relapse [2]. Therefore, the identification of feasible and sustainable interventions that can reduce MM risk and subsequent mortality is an important goal.

MM has well-defined precursor conditions which always precede the development of MM, called monoclonal gammopathy of undetermined significance (MGUS) and smoldering MM (SMM), which are relatively common blood conditions affecting ~3% of the general population over 50 years [3]. MGUS and SMM are often clinically detected through the presence of abnormal proteins called "monoclonal (M-)proteins" in the blood and/or urine; what distinguishes MGUS and SMM is their annual risk of progression. In general, MGUS progresses to overt MM at a slow rate of 1% per year, but in some patients, the risk may be as high as 58% in 20 years [4,5]. SMM has an annual risk of progression of 10%, but in some patients, risk is considerably higher [4]. SWM is a related precursor condition derived from IgM memory B cells. Similar to SMM, treatment is currently only recommended in the presence of symptoms typically associated with overt hematologic malignancy. Therefore, patients with these precursor conditions are prime candidates for blood cancer risk reduction strategies.

2.2 Clinical Management of Precursor Conditions and Status of Treatment.

The cornerstone of management for these entities is to delay therapy until progression to blood cancer, at which time patients have overt end-organ damage.[6,7] It is therefore unsurprising that patients report high levels of anxiety and distress about their conditions,[8] and cure is seldom achieved.[9] However, this paradigm may change as there are already clinical trials that show that early use of MM therapies in the precursor setting may alter the natural history of the disease[10], and importantly, may improve survival.[11] For example, in a randomized open-label phase 3 trial [11], 119 patients with high-risk smoldering myeloma were randomized to treatment or observation. Patients in the treatment group received an induction regimen (lenalidomide at a dose of 25 mg per day on days 1 to 21, plus dexamethasone at a dose of 20 mg per day on days 1 to 4 and days 12 to 15, at 4-week intervals for nine cycles), followed by a maintenance regimen (lenalidomide at a dose of 10 mg per day on days 1 to 21 of each 28-day cycle for 2 years). The primary endpoint was time to progression to symptomatic disease. Secondary endpoints were response rate, overall survival, and safety. After a median follow-up of 40 months, the median time to progression was significantly longer in the treatment group than in the observation group (median not reached vs. 21 months; hazard ratio for progression, 0.18; 95% confidence interval [CI], 0.09 to 0.32; P<0.001). The 3-year survival rate was also higher in the treatment group (94% vs. 80%; hazard ratio for death, 0.31; 95% CI, 0.10 to 0.91; P=0.03). A partial response or better was achieved in 79% of patients in the treatment group after the induction phase and in 90% during the maintenance phase. Toxic effects were mainly grade 2 or lower. Early treatment for patients with high-risk smoldering myeloma delays progression to active disease and increases overall survival. (NCT00480363).

Despite the promise of early treatment in the precursor disease setting, it has remained highly controversial given the high cost and risk of toxicity and harm to patients who may never progress to overt blood cancer.[12-14] For example, the treatments currently being investigated in the precursor disease setting carry considerable short- and long-term risks, including but not limited to arterial thromboembolic events, neutropenia and thrombocytopenia, and increased risk for secondary malignancies.[15] These toxicities, in effect, mostly limit the use of existing therapies to the highest risk patient subsets. Therefore, the identification lower-risk, cost-effective strategies to prevent disease progression in patients with less aggressive forms of MGUS, SMM, and SWM is of considerable importance.

2.3 Obesity, Excess Adiposity, and MM Pathogenesis

There is stong epidemiological and mechanistic evidence supporting the hypothesis that targeting excess adiposity is a MM prevention strategy in overweight/obese individuals with MGUS and SMM. Obesity and excess adiposity, which results in inflammation and deregulation of numerous endogenous growth factors important to MM pathogenesis, appears to be an important and consistent risk factor for MM [16-23]; it also remains the only known MM risk factor that is potentially modifiable. In an analysis of three large prospective cohorts of US adults collectively followed over 5 million person-years, we recently reported a 17% increase in MM risk per 5 kg/m^2 increase in body mass index (BMI)(HR: 1.17; 95% CI: 1.05, 1.29) [19]. Of particular relevance to the proposed project, two recent studies have demonstrated that a high BMI is associated with the malignant transformation from MGUS to overt MM [24,25]. For example, in analysis of 7,818 MGUS patients in the US Veterans Health Administration database both overweight and obesity were associated with an increased risk of transformation to MM (HR for overweight: 1.55; 95% CI: 1.16, 2.06) (HR for obesity: 1.98; 95% CI: 1.47, 2.68) [25].

Despite the consistency of the evidence regarding the association between obesity and MM mentioned above, no lifestyle modification recommendations are offered to the high percentage of MGUS and SMM patients who are overweight or obese, which population-based data suggests is upwards of 75% of MGUS and SMM patients.[25] Thus, there is a critical need to identify strategies that MGUS and SMM patients can use to control body weight and excess adiposity and minimize and the risk of disease progression to MM.[25]

2.4 Potential Benefits of Prolonged Nightly Fasting

There is considerable evidence for the human health benefits from intermittent fasting, including alternate day fasting, Ramadan, and modified fasting regimens. In rodents, intermittent fasting improves metabolic parameters, suppresses the development of cancer, and increases life span [26,27]. It is notable that these outcomes occur independent of caloric intake. In humans, we have identified numerous (>17) trials of intermittent fasting in normal weight or obese adults [28-46]. In spite of being somewhat underpowered (sample sizes ranged from 8 to 54), over 80% of the trials identified found significant decreases from baseline in weight (from -1.8% to -9.6%), as well as improvements in other cardiometabolic biomarkers. However, the majority of the fasting regimens tested to date have required extreme behavior change (e.g., fasting for 24 hours), resulting in hunger and irritability, and thereby limiting the feasibility and public health significance of these interventions.

Few studies to date have investigated the impact of a fasting regimen that is aligned with human circadian rhythms, such as a prolonged nightly fasting regimen. Nightly fasting imposes a diurnal rhythm in food intake, which appears to induce improved oscillations in circadian clock gene expression that optimizes molecular mechanisms of energy metabolism and body weight regulation [47]. Therefore, an intermittent fasting regimen that is aligned with human circadian rhythms, such as a prolonged nightly fasting regimen, has the potential to not only be more achievable and sustainable (the majority of the fasting period occurs during sleep), but in leveraging aspects of circadian biology, it also may have more robust and favorable impacts on body weight and health outcomes. In mice, an eating pattern consisting of a 16-hour fast during the inactive, predominantly "sleep," phase protects mice from obesity, hyperinsulinemia, hepatic steatosis, and inflammation [27]. In humans, observational evidence published by our team and others suggest that eating patterns that reduce or eliminate food during the nighttime hours may support weight loss, reduce the risk of some cancers, and improve aspects of metabolic health [48-52]. For example, we investigated nightly fasting and glycemic regulation in 2531 women in the National Health and Nutrition Examination Survey using time-stamped 24-hour recalls and found an increase in nightly fasting equal to 1 standard deviation (~ 3 hours) was associated with an

approximate 20% reduced odds of elevated hemoglobin A1c (OR 0.81, 95% CI 0.67, 0.97)[48]. In a separate analysis of 2,413 breast cancer survivors enrolled in the Women's Healthy Eating and Living (WHEL) Study, we found that a short nightly fasting duration (<13 hours) was associated with an increased risk of breast cancer recurrence[49] and confirmed our previous observation that a shorter nightly fast is associated with elevated hemoglobin A1c [49]. Finally, a recent single arm pilot study among 19 individuals with metabolic syndrome demonstrated that a prolonged nightly fasting regimen consisting of a 14-hours fast resulted in a statistically significant 3.3kg mean change in body weight over the 12-week intervention period [53]. Taken together, the available evidence suggests that *any* fasting schedule is likely to impact weight and metabolic processes putatively associated with carcinogenesis, and that a nightly fasting schedule may be more feasible, efficacious, and sustainable than other fasting regimens. These data motivate the proposed trial investigating a prolonged nightly fasting intervention for obesity reduction and MM/WM prevention.

2.5 Trial Rationale

2.5.1.1 Prolonged Nightly Fasting is Simple.

The current dietary guidelines for cancer prevention and weight loss focus on individual choices regarding food or food groups. While these guidelines are thought to reflect latest scientific evidence regarding diet and cancer, the likelihood that these guidelines will influence disease risk at the population-level is hindered by the difficulty that most individuals face in understanding and implementing them into their daily lifestyles. A recommendation to increase the length of the nightly fasting interval has promise to be a strategy to control body weight and reduce the risk of MM in at-risk populations given its simplicity.

2.5.2 Rationale for Investigation in Precursor MM

The cornerstone of management for both entities is to delay therapy until progression to MM, at which time patients have overt end-organ damage [6,7]. It is therefore unsurprising that patients with MGUS and SMM have shown to have high levels of anxiety and distress [54,55] and cure is seldom achieved [9]. Therefore, the identification of lower risk strategies to prevent disease progression, such as prolonged nightly fasting, is of considerable importance. Importantly, this program of research is positioned to contribute to our ability to inform improvements to the paradigm that guides the clinical care of MGUS and SMM patients, to facilitate transformation of the current watchful waiting approach,[7,13] to a paradigm focused on prevention.

2.5.3 Body Composition

New epidemiologic data indicates that body fat mass is a more valid and stronger predictor of cancer prognosis than BMI [56,57]. While BMI is used in the MM literature as a measure of obesity, there is increasing evidence that BMI is a poor surrogate measure of obesity-related entities that are relevant to disease risk and prognosis. For example, in one study of cancer-free people (N=511)[58], BMI correctly identified only 52% of obese women when obesity was determined from percent fat mass. Similarly, another study (n=88) [59] found that 46% of women with a BMI <30 kg/m^2 could be classified as obese using measures of fat mass. In clinical epidemiologic studies of obesity and cancer, including those that have been published to date in MM, this exposure misclassification can lead to biased effect estimates and obscure any true association between obesity and cancer endpoints. Therefore, additional measures of adiposity besides BMI may

provide more precise and relevant estimates of obesity and the impact of obesity-targeted lifestyle interventions.

2.6 Secondary Endpoints

2.6.1 M-Protein and Light-chain Concentrations as Clinically Relevant Disease Endpoints.
Monoclonal (M-)proteins and light chains produced in excess by an abnormal clonal proliferation of plasma (MM) cells that can be measured in the serum using Serum Protein Electrophoresis (SPEP) and the Serum Free Light Chain Assay. These quantitative tests usually correlate with overall tumor burden, and thus the SPEP is one of the most common clinical tests used to monitor patients with all stages of the disease continuum (MGUS, SMM and MM). Importantly, concentrations of these biomarkers have been repeatedly shown to reduce after treatment with a range of mild and aggressive MM therapies,[60-62] underscoring their utility as a sensitive and measurable marker of tumor response to treatment.[63]

2.6.2 Mass Spectrometry
Quantitative immunopurification mass spectrometry (QIP-MS) combines Ig immunopurification with mass spectrometry resulting in a methodology that is more sensitive and specific than serum protein electrophoresis (SPEP) and immunofixation (IFX). The technique works by first isolating Ig's using isotype specific beads. Purified Ig's are then separated into light chains and heavy chains by the addition of a reducing agent. A mass spectrometer is then used to detect a monoclonal light chain from an M-protein observed as a peak above the normal polyclonal background. Mills et al. demonstrated that QIP-MS could detect an M-protein in patient serum when SPEP and IFX were negative.[64] They also showed in serial dilution studies that a monoclonal light chain peak could be detected by QIP-MS at a level < 0.05 g/L; a level that was negative when analyzed by SPEP and IFX. The specificity of QIP-MS is provided by the superior resolving capability and mass measurement accuracy of the mass spectrometer. Barnidge and colleagues demonstrated that molecular mass could be used to monitor a specific monoclonal kappa light chain in a patient GK MM over a 7-year period.[65] The monoclonal light chain could easily be detected in samples that were negative by SPEP and IFX. Multiple clones can be easily identified in serum using QIP-MS technology since the mass spectrometer provides superior resolution compared to gel electrophoresis. M-protein quantification is performed by comparing monoclonal light chain peak intensities with an internal reference.

2.6.3 Bone Marrow Adiposity
BMAT is a newly appreciated adipose depot with endocrine and paracrine signaling functions and resides near MM cells in the bone marrow that influence the behavior and function of neighboring cells and have the potential to dysregulate normal bone homeostasis [66-68]. Obesity is usually associated with an increase in visceral and/or subcutaneous fat; however, BMAT is an understudied tissue that also responds to diet-induced changes is bone marrow adipose tissue (BMAT). Notably, there have been several studies over the past few decades that have identified BMAT as a key driver in MM progression.

2.6.4 Value of Metabolomics

Metabolomics, e.g., the high-throughput identification and quantification of small molecule metabolites produced by metabolism, can yield novel insights into pathogenesis and risk of cancer and chronic disease.[69,70] Metabolomics is the study of metabolic changes in biological systems and provides the small molecule fingerprints that reflect the complex relationships between diet, lifestyle (obesity), genes, and disease processes.[70] We believe that metabolomics offers a unique lens to study progression in the precursor MM, given that of all molecular entities (e.g., genes, transcripts, proteins, metabolites), metabolites have the closest relationship to expressed phenotype, as they are the final endpoints of biochemical processing.[71] Despite the growing interest and application of metabolomics to cancer and chronic disease research, metabolomics-based studies of MM, MGUS, or SMM/SWM are sparse.[72-77] One small study by Ludwig et al identified 25 bone marrow metabolites that differed between 10 MGUS and 10 MM patients,[72] but this work has not yet been expanded in larger samples with clinical and lifestyle data. A larger metabolomics investigation of precursor MM patients could contribute important knowledge regarding the landscape of the metabolic changes underlying the disease, and ultimately lend important insights into interception strategies and druggable targets. Particularly important categories of metabolites in cancer and metabolic disease are metabolites of glycolysis and the TCA cycle. These are of interest to the current study because of their critical role in tumor growth[78,79] and because they have been shown to be obesity related.[80] Importantly, these metabolite categories have consistently shown to be sensitive to metformin[81-83]—likely because of their relationship to the mammalian target of rapamycin (mTOR),[84,85] which is the cellular signaling cascade that serves as a master regulator of metabolism, cell growth, and proliferation.[86]

2.6.5 Quality of life in the Precursor Disease Setting

As an exploratory objective, given the high rates of anxiety and distress document in individuals with MGUS and SMM[54,55] and lack of evidence-based risk reduction strategies available for preventing disease progression to MM, we will to explore the psychosocial benefits of offering a low-risk lifestyle intervention to this patient population.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

3.1.1 BMI >= 25 kg/m^2
3.1.2 Documented diagnosis of MGUS or Smoldering MM(SMM) or Smoldering Waldenstrom Macroglobulinemia(WM) via EMR review. **note: please review case with PI or treating MD if diagnosis is uncertain.*
3.1.3 At least 18 years of age
3.1.4 Currently fasting for <14 hours per night, as assessed using 24-hour food recalls
3.1.5 Owns a cell phone and is comfortable sending and receiving text messages
3.1.6 Ability to understand and the willingness to sign a written informed consent document

3.2 Exclusion Criteria

3.2.1 Diagnosis of overt MM or WM
3.2.2 Shift Workers required to work on Night Shift
3.2.3 Patients diagnosed with another malignancy requiring active therapy
3.2.4 Clinical diagnosis of diabetes, which may increase the risk of hypoglycemia with a prolonged fast. Note: patients with diabetes may enroll with consent from MD that manages their clinical care.
3.2.5 Individuals who are pregnant are excluded from this study due to the DXA scan assessment requirement
3.2.6 Any other condition that, in the investigator's judgment, would contraindicate prolonged nightly fasting or otherwise interfere with participation in the trial, including night shift work, night eating syndrome, taking weight loss medication, or participation in another weight loss program

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

4. REGISTRATION AND RANDOMIZATION PROCEDURES

4.1 Recruitment

Participants will be primarily recruited from the Center for the Prevention of Progression (CPOP) Clinic at Dana-Farber, but we may expand recruitment to other Mass General Brigham sites. We will utilize multiple active recruitment techniques, including a pamphlet provided to participants during clinic, to maximize participation and generalizability. We will use the following strategies to identify potential participants:

- We will review clinic schedules and patient lists at DFCI and other Partners Healthcare institutions. HIPAA waivers will be obtained prior to review of these patient lists.

Once a potential participant is identified, they will be contacted by phone/email by a study coordinator to solicit interest, or during a clinic visit or through other approved methods of communication.

Interested subjects identified through these recruitment strategies will be pre-screened by study staff either in person or by phone initially and if potentially eligible, he or she will meet with a member of the study staff to review the protocol and sign informed consent.

Consenting will occur in person, by mail, or remotely via 45 CFR part 46, local CON-100 and 21 CFR part 11 compliant Adobe eSign or REDCap eConsent. Whenever possible, remote consenting by phone and mail or by electronic signature will be performed prior to the patient's standard of care clinical appointments at DFCI to minimize time and extraneous staff at DFCI during the COVID-19 pandemic. The use of electronic consent (e-consent) to obtain consent

remotely will allow us to enroll participants to the study using a distance-based approach that

allows patients to feel safer and reduces the number of visits patients have to make to Dana-Farber. An e-consent process will allow us to streamline the consent process and will help DFCI with its goal of minimizing the number of people on clinic floors at this time. Participants that are consented electronically, via either Adobe eSign or via REDCap eConsent, will be provided with a copy of the consent form to review before having a scheduled phone or video call to go over the consent form in detail and discuss any potential questions with study staff. Once review of the consent has concluded, the study staff will email another consent form via Adobe Sign or REDCap eConsent through an official Dana-Farber email to the participant's authenticated and confirmed email address that is on file in their medial record.

4.2 Registration process

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of any protocol-specific therapy or intervention. Any participant not registered to the protocol before protocol-specific therapy or intervention begins will be considered ineligible and registration will be denied.

A member of the study team will complete the protocol-specific eligibility checklist.

The eligibility checklist(s) and all pages of the consent form(s) will be faxed or emailed to ODQ at [redacted]. The ODQ will (a) review the eligibility checklist, (b) register the participant on the protocol, and (c) randomize the participant.

Randomization can only occur during ODQ business hours (8:30am - 5pm Eastern Time, Monday through Friday excluding holidays).

The ODQ Protocol Systems Coordinator is responsible for randomizing subjects to treatment arms for investigator-sponsored research

The statistician in the Department of Biostatistics and Computational Biology provides ODQ with any necessary randomization sheets and instructions specific to the protocol.

An email confirmation of the registration and/or randomization will be sent to the study coordinator(s) from the registering site, treating investigator and registering person immediately following the registration and/or randomization.

Following registration, participants may begin protocol-specific therapy and/or intervention. Issues that would cause treatment delays should be discussed with the Principal Investigator (PI) of the registering site. If the subject does not receive protocol therapy following registration, the subject must be taken off study in the CTMS (OnCore) with an appropriate date and reason entered.

4.2.1 Registration Process for DF/HCC Sites

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

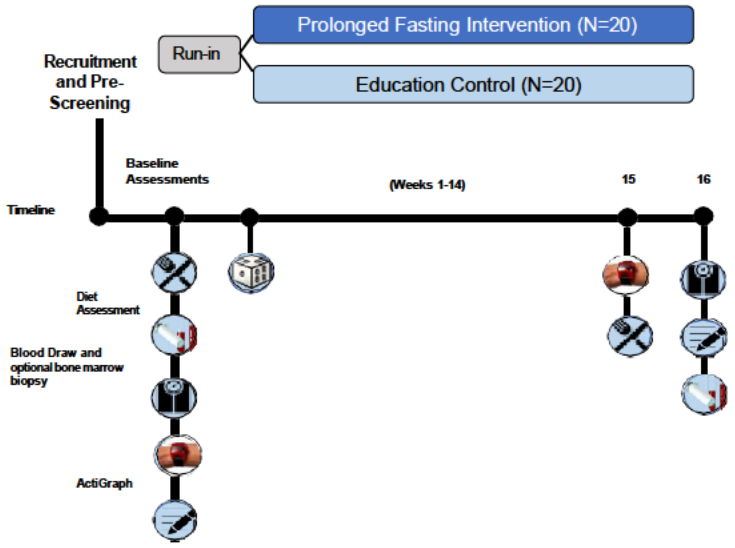
Following registration, patients will be randomized to the intervention/control condition. Initiation of the intervention/control condition should begin ideally no later than 4 weeks of screening assessments.

5. INTERVENTION PLAN

We will conduct a 4-month randomized trial of our prolonged nightly fasting intervention (PROFAST) in 40 overweight and obese patients with MGUS, SMM, or SWM. We focus on these individuals because they have multiple risk factors for hematologic malignancy but lack evidence-based strategies to prevent progression to overt malignancy. The goal of the study is to acquire preliminary outcome data suggesting the efficacy of a prolonged nightly fasting intervention on "white" adipose tissue and clinical signs of disease progression in MGUS and SMM/SWM patients; we will also explore the degree to which the intervention impacts adiposity in the bone marrow niche. Participants will undergo assessments of diet, physical activity, body composition, as well as collection of blood and bone marrow at baseline and 4-months.

The intervention is designed to promote a 14-hour fast during the nighttime hours. The intervention will draw from established behavioral change theories, and the mode of delivery will be through telephone counseling and a simple text messaging system.

A schematic representation of the study design is shown below:



5.1 Unblinding

NA

5.2 Intervention Regimens

Details of the Prolonged Nightly Fasting Intervention. The intervention goal is to achieve a 14-hour nightly fast. A 14-hour window was selected because it has been demonstrated to be an achievable intervention target in other populations of adults with chronic health conditions, and studies to date suggest it is a sustainable intervention target. Specifically, previous interventions have reported elective continuation of the intervention beyond the intervention period, resulting in sustained health benefits including weight loss [53,87]. The overnight fasting period will be defined as the longest interval of time overnight in which no calorie-containing foods or beverages are consumed. Given our prior findings that fasting may be more beneficial when aligned with the biological night [50], participants will be encouraged to begin their nightly fast by 8 pm. To maximize acceptability and adherence to the intervention protocol, participants will be allowed to consume non-caloric beverages including water, plain coffee, plain tea, zero-calorie sodas, and calorie-free sweeteners.

The intervention is informed by several behavior change theories and incorporates a number of theory-based behavioral strategies in its design. Constructs targeted by the intervention include self-monitoring and intention formation as well as goal setting and goal review, feedback on performance, building self-efficacy, and discussions of benefits, barriers and problem-solving. The intervention will consist of a health coach-supported initial phase during weeks 1-4 of the intervention period, followed by a gradual transition to activities that promote self-reliance for behavioral maintenance beginning week 4 until the end of study.

During weeks 1 and 2, participants will be required to engage in two brief (~30-min) phone calls per week with a trained health coach, who will review the benefits of a prolonged nightly fasting schedule, discuss the participant's personalized fasting goals (see below), and discuss barriers to achieve the intervention goal. All participants will be provided with a workbook to support the intervention, recording of fasting times, and health coach discussions (see Appendix). The health coach will also provide feedback on performance, emphasizing the positive and building self-efficacy. Participants will be encouraged to report difficulties or challenges in meeting the intervention target and will be provided strategies to overcome any challenges reported. During weeks 3-4, calls will be reduced to once per week. In addition to the calls with the health coach, a text messaging system will be used for self-monitoring and to encourage more prolonged nightly fasting intervals. The text messaging system will be used throughout the duration of the study.

Week	Intervention Activities	Behavior Change Constructs Targeted
1-2	2 counseling calls/week Bedside Journal	○ Intention formation ○ Goal setting and goal review ○ Self-monitoring ○ Benefits, barriers and problem solving ○ Feedback on performance
3-4	1 counseling call Send/receive text messages (week 4)	○ Intention formation ○ Goal setting and goal review ○ Self-monitoring ○ Benefits, barriers and problem solving ○ Feedback on performance ○ Self-efficacy
5-16	Send/receive text messages	○ Self-monitoring ○ Feedback on performance ○ Self-efficacy

Fasting Goals by Week: Fasting goals during the initial weeks of the study will be individualized, allowing participants to gradually work up to a 14-hour fasting duration on or before the third week of study. An example of individualized fasting plans for weeks 1-4 are shown below:

Baseline fasting duration of <12 hours per night	
Week	Hours
1	12
2	13
3	14
4	14 (maintenance)

Baseline fasting duration of 12 hours per night	
Week	Hours
1	13
2	14
3	14 (maintenance)
4	14 (maintenance)

Baseline fasting duration of 13 hours per night	
Week	Hours
1	14
2	14 (maintenance)
3	14 (maintenance)
4	14 (maintenance)

Details of the Text Messaging System: For the text messaging component, participants will be asked to text the study team to indicate when they began and ended their overnight fast. This will provide a means of monitoring adherence to the intervention protocol in real-time. Participants will receive an automatic response to their messages with positive reinforcement if the fasting goal was successfully achieved, or corrective tools such as a behavioral strategy that may help them achieve a longer fast. The messages sent back to participants will contain feedback about their cumulative adherence to the prolonged overnight fasting pattern, calculated as the percentage of the successful overnight fasts attempted at that point in time. Participants will also receive a text message each day to remind them of their target end time of the overnight fast, as well as encouraging text messages to promote adherence that are customized to past performance; health coaches will also have the ability to customize messages to participants that have difficulty adhering to the intervention schedule. An example of text messages that will be sent to participants through the automated text messaging system is provided in the table below. The text messaging system will be administered through a platform provided by Mosio Incorporated (San Francisco, CA), which allows for direct integration of text messaging and adherence data into RedCap.

Example Text Message interaction with a study participant

Time Stamp	Message Type	Message
2/17/13, 6:00PM	Sent	Remember: Calories break a fast! Once you start, you need be calorie-free ☺
2/17/13, 7:28PM	Received	FAST
2/17/13, 7:29PM	Response	Thanks! You are now running calorie free! Check back in the morning for your end time.
2/18/13, 7:00AM	Sent	Your fast ends at 9.28am. You can do it!
2/18/13, 9:55AM	Received	EAT
2/18/13, 10:05AM	Response	Congratulations! Your success rate to date is 100%. Nice work!

Healthy Lifestyle Education Control. We will administer educational information to the control arm of the trial as a means to enhance the retention of participants randomized to this group (see Control Workbook in the Appendix). At baseline, control participants will receive an educational session with the health coach. It is notable that research indicates that a single education session has only modest and temporary impacts on behaviors and weight loss among most individuals [88,89]. To support sustained engagement throughout the 4-month study period, control group participants will receive weekly emails highlighting heathy lifestyle topics such as healthful diets and increasing physical activity and one text message per week using the same text messaging system that participants in the intervention receive. These text messages will contain a mixture of educational information and may contain personal touch points to make participants feel valued. At the end of the 4-month study period, participants in both the intervention and education control group will receive a $50 gift card upon completion of the End of Study visit to promote study retention. Both the intervention and education control group will also receive parking vouchers, if needed, at the Baseline visit and End of Study visit.

5.3 General Concomitant Medication and Supportive Care Guidelines

Participants may receive any supportive care necessary to address side effects of fasting so long as it is not considered investigational

5.4 Prohibited Medications and Procedures

Participants are prohibited from taking any investigational medications, or any cancer directed therapy during the study (bone health medications are acceptable). In the event that a cancer-directed therapy is clinically warranted (e.g., progression to MM/WM), participants will come off study so that appropriate care can be received.

5.5 Removing a Participant from Intervention

In the absence or withdrawal from the intervention, it may continue for up to 4 months, or until disease progression to overt MM/WM. If intervention activities discontinue, the reason for removal from protocol intervention, and the date the participant was removed, must be documented in the case report form (CRF).

When a participant is removed from protocol intervention and/or is off of the study, the participant's status must be updated in OnCore in accordance with REGIST-OP-1.

5.6 Duration of Follow Up

The total study intervention period is 4 months, with the final assessment occurring at the end of the 4-month intervention period. There is no planned follow-up once patients have completed the end of study visit.

5.7 Removing a Participant from Study (Off Study/Off Follow Up)

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Death
- Progression to overt MM

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF). In addition, the study team will ensure the participant's status is updated in OnCore in accordance with REGIST-OP-1.

6. DOSING DELAYS/DOSE MODIFICATIONS

N/A

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

7.1 Expected Toxicities

7.1.1 Adverse Events List for Fasting

• Participants may experience lightheadedness, headaches, restlessness, irritability, and low blood glucose.

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
  - Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-

Specific Expedited Adverse Event Reporting Exclusions.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study intervention.
  - Probable – The AE *is likely related* to the study intervention.
  - Possible – The AE *may be related* to the study intervention.
  - Unlikely – The AE *is doubtfully related* to the study intervention.
  - Unrelated – The AE *is clearly NOT related* to the study intervention.

7.3 Adverse Event Reporting

7.3.1 Although this is not expected, the event of an unanticipated problem or life-threatening complications the study team must immediately notify the PI.

7.3.2 Investigators **must** report to the PI any adverse event (AE) that occurs during the intervention.

7.3.3 Adverse Event Reporting Guidelines

The table below indicates which events must be reported:

- **CTCAE Grade 2 and Grade 3 Events** – that are Unexpected and there is a Reasonable Possibility that the Adverse Event is related to the study intervention.
- **CTCAE Grade 4 Events** – Report all events that are Unexpected. Events that are Expected and listed within the protocol and/or current consent form do not need to be reported to the DFCI IRB. Please note, an event that presents at a higher severity than what is currently listed within the protocol and/or current consent as expected would be considered unexpected and reportable.
- **ALL CTCAE Grade 5 Events**

7.3.4 Protocol-Specific Adverse Event Reporting Exclusions

Only events that are considered possibly, probably or definitely related to the intervention will be captured on the database for the purpose of this study.

7.4 Reporting to the Food and Drug Administration

NA

7.5 Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports, sentinel events or unanticipated problems that require reporting per institutional policy.

7.6 Routine Adverse Event Reporting

Any Adverse Events related to the intervention **must** be reported in routine study data submissions to the PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB) must also be reported in routine study data submissions.**

8. PHARMACEUTICAL INFORMATION

NA

9. STUDY MEASURES

9.1 Screening/Baseline Assessments

Pre-screening:
Preliminary assessment of eligibility will be conducted in person or via the telephone using the templated screening script (see appendix). Individuals who are interested in participating and appear eligible will then be invited to speak with study staff so that details of the study can be explained, answer any questions the participant has, as well as review and sign the informed consent form.

Baseline Clinic Visit. After the prospective participant signs the informed consent form, a more thorough review of eligibility will be assessed. This includes a physical assessment, and dietary assessment. Participants will then be asked to complete the following:

- Physical Assessment. Height and weight will be measured in duplicate.
    - Weight: Each participant will be weighed on a medical balance or electronic scale in light clothing without shoes. Participants will be asked to empty their pockets and remove and heavy jewelry or accessories. Participants are weighed on the same scale throughout the study. Before each weighing, the scale zeroed and set to read results in kilograms. If the participant's feet are bare, a paper towel will be placed on the scale platform. The participant will be asked to stand still on the scale platform, arms down at her sides, and feet centered on the platform with weight evenly distributed. Weight is recorded to the nearest 0.1 kg (rounding down).
    - Height: The participant's height will be measured without shoes, using a stadiometer. The participant will be asked to stand up with heels together and weight equally distributed. Ideally, his/her heels, buttocks, shoulders, and head should all touch the vertical board; however, in some cases this may not be possible. In this event, the measurement will be taken with buttocks and heels touching the vertical board. The participant will be asked to breathe in deeply and the study staff will place the headboard on the participant's head with only enough pressure to slightly compress the hair. Height will be recorded to the nearest 0.1 cm (rounding down).

- Clinical Labs. Clinical labs will be scheduled as part of the patient's routine clinical care and may be subject to the discretion of the ordering provider but should include SPEP, SFLC and hemoglobin.

- Research blood draw. Research blood will be collected at baseline and 4-months. Collection of blood specimens for analysis will be obtained at the times of standard of care

blood draws, whenever feasible. These orders may be shared with biobanking protocol 14-174 to minimize the number of research samples collected on a patient in a single day. To the extent possible, these will be scheduled at the time of any stand of care collection to minimize burden to the participant. Any sample collected on this trial that has not been exhausted for the purposes of the aims detailed in this study will be stored for future use. Specimens will be collected and subsequently processed, analyzed, and stored at Dana-Farber Cancer Institute at the following address for the Ghobrial Lab:

Ghobrial Lab
Dana-Farber Cancer Institute
[redacted]
Boston, MA 02215

Suggested specimen include:

- 2x 10ml Purple Top Tubes (K2EDTA)
- 1x 6ml Red Top Tube (no additive)
- Tubes types may be substituted if requested by the study team

- Bone marrow aspirate/biopsy. Research collection of bone marrow for analysis will be obtained at baseline and 4-months as a standard of care procedure, unless refused by the participant or their physician. These collections are highly encouraged but are considered optional. As stated previously, sample collection orders may be shared with biobanking protocol 14-174 to minimize the number of research samples collected on a patient in a single day. Any sample collected on this trial that has not been exhausted for the purposes of the aims detailed in this study will be stored for future use. Specimens will be collected and subsequently processed, analyzed, and stored at Dana-Farber Cancer Institute at the following address for the Ghobrial Lab.

  Suggested specimen include:

  - 2x10mL Purple Top Tubes (K2EDTA)
  - Tubes types may be substituted if requested by the study team

- DXA scan Appendicular fat free mass (AFFM) will be measured from a whole-body, hip and spine scan using Dual-Energy X-ray Absorptiometry (DXA Hologic model Horizon W, serial # is 303895M). Predicted AFFM will be calculated using the following equation: -14,529 + (17,989 x height in m) + (0.1307 x total fat mass in kgs). Lean mass, fat mass, and body fat % will also be obtained from the whole-body DXA scan. Scans will be covered by study funds.

- Two 24-hour dietary recalls. Participants will undergo two 24-hour dietary recalls at this timepoint. Recalls will be conducted through the Behavioral Measurement and Interventions Shared Resource (BMISR) at the University of Arizona (UA) Cancer Center. Scheduling will be coordinated by staff at DFCI to ideally collect 1 weekday and 1 weekend day recall. Interviews will assess food and beverage consumption over a 24-hour period, including the timing of intake, using the USDA multi-pass method with the University of Minnesota Nutrition Data System-Research Version (NDS-R) system.

- 7-day accelerometer wear period. Participants will also be asked to wear an ActiGraph accelerometer on their wrist for 7 days for a baseline assessment of sleep, activity, and to approximate circadian rhythm parameters [90-92]. An ActiGraph accelerometer is a small device used by researchers to capture and record continuous, high resolution physical activity and sleep/wake information. It is notable that unlike other wrist-worn physical activity and sleep devices, participants cannot see the data being collected, and the research

team can only access data via a USB connection. Therefore, data cannot be viewed in real time, and the device does not capture location data.

- Baseline Questionnaire. Participants will be asked to complete questionnaire via print or online that ascertains information about quality of life, lifestyle, and demographics and medical comorbidities using a variety of well-validated measures described below:

    - Quality of life: will be assessed using the well-validated PROMISE global health survey [93-96]
    - Self-reported physical activity: will be assessed with the Global Physical Activity Questionnaire (GPAQ).[97] The GPAQ calculates metabolic equivalents (METs) to express the intensity of self-reported physical activities. The GPAQ has good reliability (Kappa=0.67 to 0.73; Spearman's rho=0.67 to 0.81) and has been validated with the International Physical Activity Questionnaire in the general population,[98] and against objective accelerometer measures in population sub-groups.[99]
    - Cancer worry: will be assessed using a 4-item scale adapted from Lehrman and colleagues [100].
    - Sleep impairment and disturbance: will be assessed using 8-item short forms available through the Patient-Reported Outcomes Measurement Information System (PROMIS™), which is part of a National Institutes of Health Roadmap initiative for measuring patient-reported outcomes.[101] An additional 3-item measure was included to assess sleep duration, insomnia (yes/no), and narcolepsy (yes/no/unsure).
    - Smoking and alcohol: use will be assessed via questions developed by Willet and colleagues for cancer epidemiology cohorts (refs)[102,103].
    - Other information collected at baseline include sociodemographic and medical comorbidities.

Participants meeting eligibility criteria and who completed the above assessments will be randomized to the intervention and will be relayed this information ideally within 5 business days of randomization unless a later date is requested by the participant. Please note that participants unwilling/unable to complete a bone marrow biopsy will be permitted to be randomized to the study.

9.1.1 Pregnancy Screening

For women of child-bearing potential, a spot urine pregnancy test will be collected at Baseline and End of Study prior to performing DXA scans. A pregnancy test can be waived in certain conditions, such as post-hysterectomy. As noted in Exclusion Criteria 3.2.5, “Individuals who are pregnant are excluded from this study due to the DXA scan assessment requirement.” Although radiation from DXA Scans is relatively minimal, the frequency of these exams is slightly greater than what patients would receive as standard care. Therefore, there is an elevated risk of radiation exposure if the participant is pregnant at the time DXA scans are performed.

9.2 Final assessments

A final clinic visit will be scheduled for the 4-month time point so that weight, patient reported outcome measures, DXA scan, and sample collection and clinical labs can be repeated. Participants will also be asked to complete two 24-hour dietary recalls, wear a 7-day accelerometer, and take the Final Questionnaire, which is an abbreviated version of the Baseline Questionnaire. In addition to the Final Questionnaire, participants randomized to the Fasting Intervention will also be asked to complete an anonymous debriefing survey within SurveyMonkey. This survey will not include any personal information but will ask participants about how helpful certain aspects of the study were, including coaching calls and the text messaging system. Participants can also take this survey in person, but as noted above, personal information will not be documented on the paper version of the questionnaire.

9.3 Endpoint assessment

Primary endpoints of the trial are changes in body composition, assessed via whole body DXA scans from baseline to 4-months.

9.4 Correlative Studies

No correlative studies are planned outside the study primary and secondary endpoint assessments.

10. STUDY CALENDAR

Registration and randomization should be conducted within 28 days (4 weeks) of baseline assessments. End of study assessment should ideally be completed within 7 days of completing study intervention. Assessments, including the physical assessment and two dietary recalls, must be performed prior to randomization to the intervention and only after signing consent unless done as part of standard of care procedure.

	Screening/ Baseline	End of Treatment Visit [6]	EDC Timepoints
Informed consent	X		N/A
Questionnaire/Survey[1]	X	X	Baseline and Final Visits
Height	X		Baseline
Weight	X	X	Baseline and Final Visits
Clinical labs [2*]	X	X	Baseline and Final Visits
Spot Urine Pregnancy Test (if applicable)	X	X	Baseline and Final Visits
DXA Scan	X	X	Baseline and Final Visits
24-Hour Dietary Recall	X	X	Baseline and Final Visits
7-Day Accelerometer	X	X	Baseline and Final Visits
De-Briefing Survey[3]		X	Final Visit (Fasting Arm ONLY)
Bone Marrow Aspirate and Core[4]	X	X	If a bone marrow biopsy or aspirate is performed clinically at any time during the study as part of SOC, it should be captured in Inform
Research Blood Collection[5]	X	X	Baseline

1 Questionnaires may be completed in person, ,by mail, through RedCap, or other acceptable method.

2 Labs will be billed to insurance as part of routine care and should include SPEP, SFLC, and Hgb but are subject to discretion of the MD of the patient.

3 De-Briefing Survey for Fasting participants only. Anonymous survey completed via SurveyMonkey

4 Research bone marrow samples are not required but highly encouraged. Research bone marrow aspirate sample will be collected if bone marrow is performed clinically (standard of care); However, participant may refuse collection.

5 Research blood sample collection at the time of routine clinical blood draw

6 End of Study assessments should ideally be done within 7 days of the end of intervention period.

*data collection may be waived with written consent from PI

11. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

11.1 Data Reporting

11.1.1 Method

All study data, including medical record review data and data collected from participant questionnaires, will be stored in a password-encoded RedCap database. RedCap is HIPAA compliant and password protected. For participants that choose to answer questionnaires electronically, their questionnaire answers will be saved directly into RedCap. Data from paper questionnaires will be entered by study staff into the RedCap database. If a participant completes questionnaires via paper, these paper copies of surveys will be stored in locked cabinets in a secured office that only the study team will be able to access.

11.1.2 Responsibility for Data Submission

Investigative sites are responsible for submitting data and/or data forms within the RedCap database in accordance with DF/HCC policies.

11.2 Data Safety Monitoring

Not Applicable.

12. STATISTICAL METHODS

12.1 Study Design/Endpoints Sample Size and Power

Although the proposed research is a pilot study, with our sample of N=40, assuming a standard deviation of 3.8%[104] we will have 80% power to detect a between group difference of approximately 3.5%, with a type 1 error rate of 0.05. For M-protein, assuming a baseline concentration of 7.23 g/dL, a standard deviation of 0.97 g/dL – which are values derived from a representative sample of MGUS and SMM patients at Dana-Farber – we will have 80% statistical power to detect a between group difference of 0.87 g/dL with a type 1 error rate of 0.05, which is a difference that is considered clinically meaningful [105,106].

12.2 Statistical Analysis

The key outcomes we are specifically powered to evaluate in this trial are changes in body composition (with a focus on visceral and subcutaneous adiposity), M-protein concentrations, and bone marrow adiposity. Changes in these endpoints will be evaluated from baseline to follow-up in the two groups using a repeated measures mixed-effects model that accounts for the

correlation between baseline and follow-up measures and is generally robust to missing data. The baseline value of the dependent variable (e.g., weight, M-protein level) and disease subtype will be included as covariates in the regression models. Group-by-time interaction terms will be included as fixed-effects in the regression model. Model fit will be assessed using standard methods. In consideration of sex as a biological variable and disproportionate impact of MGUS and SMM on males compared to females, we will examine effect modification by sex. Analysis of this endpoint will utilize intention-to-treat methods [107].

12.3 Sample Size, Accrual Rate and Study Duration

We expect to enroll approximately 3-4 patients per month into the study for the first year of the study. Follow-up assessments are projected to commence in year 2. Accrual targets are outlined below:

Accrual Targets					
Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino	2	+	3	=	
Not Hispanic or Latino	18	+	17	=	
Ethnic Category: Total of all subjects	(A1)	+	(B1)	=	(C1)
Racial Category					
American Indian or Alaskan Native	0	+	0	=	
Asian	1	+	0	=	
Black or African American	5	+	6	=	
Native Hawaiian or other Pacific Islander	0	+	0	=	
White	14	+	14	=	
Racial Category: Total of all subjects	(A2)	+	(B2)	=	(C2)
	(A1 = A2)		(B1 = B2)		(C1 = C2)

12.4 Stratification Factors

None

12.5 Interim Monitoring Plan

Refer to section 11.2

12.6 Analysis of Primary Endpoints

Refer to section 12.2

12.7 Analysis of Secondary Endpoints

The secondary endpoint of this trial will be changes in a variety of biomarkers detailed in section 1.2. Changes in continuous variable outcomes will be evaluated from baseline to follow-up in the two groups using a repeated measures mixed-effects model that accounts for the correlation between baseline and follow-up measures and is generally robust to missing data. The baseline value of the dependent variable and disease subtype will be included as covariates in the regression models. Group-by-time interaction terms will be included as fixed-effects in the regression model. Model fit will be assessed using standard methods. All primary analyses will utilize intention-to-treat methods.[107]

Metabolite features will be analyzed as measures of peak areas, which are proportional to feature concentration and can be compared for any given metabolite. The metabolite variables will be standardized to a mean of 0 and standard deviation of 1.

12.8 Reporting and Exclusions

NA

13. PUBLICATION PLAN

The results should ideally be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors.

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