Nutritional (High Protein) Perihabilitation Intervention in Older Veterans Undergoing Surgery

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Purpose

The purpose of this research is to evaluate the feasibility, fidelity, and acceptability of a perioperative protein-enhanced intervention compared to a standard protein intervention. The successful completion of the proposed research will provide preliminary data to test this hypothesis in a large scale randomized controlled trial. Such findings would be of considerable importance, providing a patient-centered viewpoint that will inform the development of nutrition interventions that meet the standards and needs of high-risk Veteran Populations.

Specific Aims

Specific Aim 1.1 *- Use a pilot trial to evaluate the feasibility, fidelity, and acceptability of a perioperative protein-enhanced intervention compared to an educational, normal protein control.*

Introduction. Malnutrition is recognized as a major concern by healthcare providers, as well as by patients, families, and caregivers. In a very recent survey, 28% of 1,035 patients, families and caregivers reported that malnutrition was a very significant problem, while 55% reported it was a somewhat significant problem in older adults 65 and older.[26] This response aligns with reports that up 65% of older adults admitted to the hospital are malnourished (National Resource Center on Nutrition, Physical Activity, and Aging, 2015). Thus, it is essential to establish systematic malnutrition screening in the clinical setting and to develop intervention models and standards of nutritional care. The *objective of this aim* is to investigate the feasibility, fidelity and acceptability of a nutrition intervention protocol providing higher protein intakes before and after surgery in malnourished Veterans. To achieve the objective of this aim, we will test our working hypotheses that recruitment in clinic will have a high yield and that intervention fidelity (adherence, retention) and acceptability (attrition, patient satisfaction) will be predominantly satisfactory. The *rationale* for this aim is that successful completion of the proposed research will provide necessary knowledge to begin to identify feasible and acceptable interventions for community-dwelling Veterans who are preparing for surgical procedures. When the proposed studies for Aim 1.1 have be completed, it is our *expectation* that ≥75% of patients approached for recruitment will agree to participate, ≥75% of the time patients will adhere to the intervention, ≥80% of the participants will remain in the study, and that ≥80% of participants will find the intervention to be acceptable. Such findings would be of considerable importance, providing a patient-centered viewpoint that will inform the development of nutrition interventions that meet the standards and needs of high-risk Veteran Populations.

Specific Aim 1.2 *– To determine the effect size for planned future studies of enhanced protein supplementation in malnourished Veterans, with physical function as the primary outcome of interest. Of secondary interest are: biomarkers of inflammation (albumin, hsCRP, TNF-α, IL-6), dietary intake, hospital readmission, discharge location, length of skilled care, and ED admission, and physical activity.*

Introduction. Older adults have reduced adaptive and regenerative capacities to recovery from a surgical insult.[27] Thus, when coupled with insufficient energy intake, malnutrition becomes the driver that leads to further deterioration of functional abilities, reduction in lean muscle mass, and inability to maintain physical reserve. A generous and balanced intake of high quality protein (~30 grams) is essential for achieving optimal protein synthesis in older adults[28] and is linked to lean mass retention.[29] The essential amino acids

found in complete (animal) proteins stimulate translation initiation of the mTOR signaling pathway and increase muscle protein synthesis in older individuals.[29] The *objective of this aim* is to research the effects of a meal-based protein enhanced perihabilitation intervention in malnourished older Veterans undergoing elective surgery on the primary outcome physical function and secondary outcomes, inflammatory biomarkers (albumin, hsCRP, TNF-α, IL-6), dietary intake, hospital readmission, discharge location, length of skilled care, and ED admission, and physical activity. To achieve the objective of this aim, we will test the *working hypothesis* that Veterans consuming the enhanced protein supplementation will have superior improvements in function compared to the control arm. *Approach:* We will further refine our working hypothesis in a two-armed pilot trial comparing a high protein nutrition supplement for two weeks pre and post-surgery to an education control arm. We will assess physical function (SPPB) and secondary outcomes two weeks before, the day of surgery, and four weeks post-surgery. The successful completion of the proposed research will provide preliminary data to test this hypothesis in a large scale randomized controlled trial. When the proposed studies for Aim 1.2 have be completed, it is our *expectation* that the protein intervention will prove to provide higher functional and physiological benefits relative to the control treatment, illustrating the importance of nutritional perihabilitation prior and following surgery in high-risk, vulnerable populations.

Design

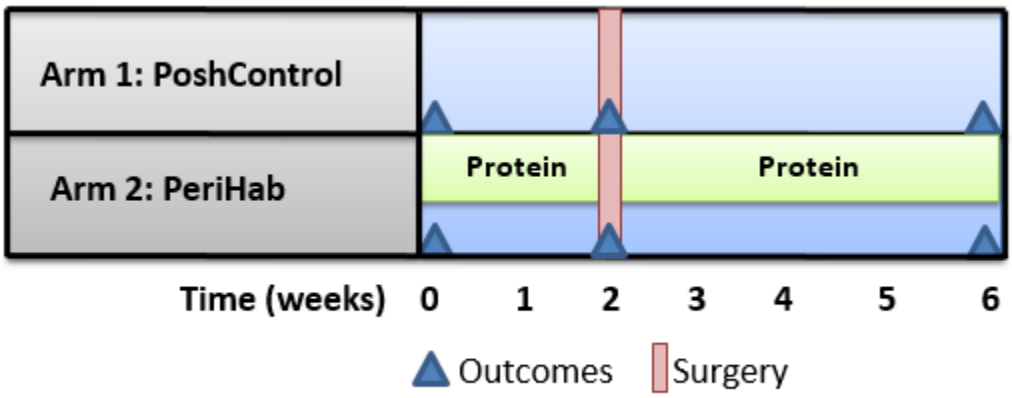
This is a Randomized Controlled Study. Veterans will be enrolled until 84 participants have completed the study.

Setting: The POSH Clinic is an interdisciplinary collaboration between surgery, anesthesiology, geriatrics, nursing, and physical therapy to provide perioperative surgical care for high-risk Veterans at the Durham VAMC. The clinic opens with a conference to review patients to be seen that day. The surgery chief resident presents and the team covers technical issues with the surgery and selection of anesthesia, as well as covering a list of specific care points. The POSH clinic estimates 200 – 400 patients enrolled annually.

VAPOSH Veterans who are malnourished or at risk of being malnourished will be randomly assigned on a 1:1 ratio by computer-generated random numbers to either an education (nutritional counseling) control (PoshControl) arm or high-protein perihabilitation (PeriHab) arm. All will receive nutrition education. Participants in the PeriHab arm will also be provided with high quality protein supplements that will bring their protein intakes to at least 30 grams for each of the 3 meals per day.

Study Arms:

- PoshControl; n = 42: During their VAPOSH clinic visit, participants will be provided nutrition counseling and prescribed to consume protein at 1.0 g/kg of body weight in the form of educational handouts explained by a Registered Dietitian. Participants will also be instructed to consume 1 oral nutrition supplement per day two weeks before surgery.
- PeriHab; n = 42: PeriHab will be provided nutrition counseling and prescribed to consume protein at 1.6 g/kg of body weight) as well as provided 30 g of high quality protein to some 3 times per day for 2 weeks before and 4 weeks after surgery.



Measurements:

After the participant has been consented and HIPAA Authorization forms have been signed, a Registered Dietitian will administer the NRS-2002 screening tool, the PG-SGA, and nutrition focused physical exam. A patient screening "nourished" on the NRS-2002, PG-SGA, and nutrition focused physical exam will not be included in the study. For study candidates who are malnourished or at nutritional risk we will then proceed with baseline assessments (described below). Upon the completion of all baseline assessments, the participant will be randomized to PeriHab or PoshControl. The following variables will be blocked in this order: 1) surgery type and 2) American Society of Anesthesiology (ASA) Physical Status Classification System (≥3 versus <3). An equal number of participants will be randomized across the two arms.

Measures and Data Collection Points

Measure	**When Collected**
NSR-2002	Baseline (T1), T2, T3
PG-SGA	T1, T2, T3
Nutrition Focused Physical Exam	T1, T2, T3
Cognition	T1
Medical History	T1
Demographic	T1
Anthropometrics	T1, T2, T3
Comorbidity Status	T1
Bristol Stool Chart	T1
Short Physical Performance Battery	T1, T2, T3
Handgrip strength	T1, T2, T3
Biological Markers	T1, T2, T3
Postoperative outcomes	T3

Physical Activity	T1, T2, T3
PROMIS and PROMIS GLOBAL QUESTIONNAIRES	T1, T2, T3
Three-day Food Record	T1, T2, T3
Protein Checklist	Daily
24-Hour Dietary Recall	Weekly between time points
Participant Satisfaction Questionnaire	T3
Participant Acceptability	T3

Risk/Benefit Assessment

There are no known psychological hazards or risks associated with completing the nutrition screen and assessment questionnaires. The nutrition-focused physical exam will involve palpation of the Veteran to identify edema, skin or muscle changes, fat loss, and muscle wasting and muscle strength that may be uncomfortable or cause some distress. To minimize this risk, the Registered Dietitian conducting the nutrition-focused physical exam will have completed a hands-on workshop offered by the Academy of Nutrition and Dietetics prior to administering the physical exam. The physical performance tests include activities such as walking, standing, and stepping. These activities reflect common activities of daily living and as such, are associated with minimal risk for injury. However, there is a small risk of falls or muscle soreness with physical testing. To minimize risk, trainer personnel will oversee physical performance testing at all times. There is potential risk associated with venipuncture, taking blood from a vein in the arm by needle stick. Risks associated with drawing blood from the arm include momentary discomfort and/or bruising. Infection, excess bleeding, clotting, or fainting are also possible, although unlikely. Blood draws will be done by a trained phlebotomist and every effort will be made to prevent discomfort. There is a potential risk associated with the loss of confidentiality of the study data. However, of primary importance in all study activities will be the security and protection of Veterans' private health information (PHI). All staff will complete educational modules designed to improve good clinical practices, improve protection of participant privacy, and promote information security and research compliance.

Participants may benefit from this study by improving their nutritional status and functional status during the perioperative period. Additionally, participants may benefit from knowing that their participation in research will provide valuable information regarding the nutritional status of older Veterans preparing for surgery, and will allow for better identification and management of Veterans at nutritional risk before and after surgery.

Selection of Subjects

The inclusion, exclusion criteria are outlined below:

Table 2. Inclusion/Exclusion Criteria	
Inclusion Criteria	**Exclusion Criteria**
• Referred to VAPOSH (at increased risk for post-operative complications) • Abdominal surgery (upper GI, colorectal, hepatobiliary, pancreatic, intra-abdominal,	• Living in skilled nursing facility • Having any surgery other than abdominal surgery • A score of <21 (high school edu.) or <20 (less than high school edu.) on the Montreal Cognitive Assessment (MoCA) or Saint Louis

bladder, VATS/lobectomy and abdominal aortic aneurysm) • Age ≥ 60 years • Malnourished or at nutritional risk (PG-SGA and Nutrition Focused Physical Exam) • English speaking	University Mental Status (SLUMS) and inability to preform 1 or more activities of daily living (ADL). • A diagnosis of Galactosemia, a rare genetic metabolic disorder that affects an individual's ability to metabolize the sugar galactose properly.

Only participants scheduled for a POSH clinic visit will be eligible for study participation. Dr. Starr or study staff will meet with the coordinator of the POSH clinic, weekly to identify eligible patients. We will screen and consent individuals until we meet the desired sample size of 84 subjects. The POSH clinic has over 300 visits annually.

To protect vulnerable populations or those subjects who may be susceptible to coercion or undue influence against, any Veteran who is approached by staff will be told that their participation is voluntary, and they may choose not to answer any questions that they find too sensitive. Also, Veterans will be told that their participation will not affect their care at the VA. The study staff member will explain the study in detail. No study procedures will begin until formal, written informed consent has been obtained.

Subject Recruitment

This study will utilize a Request for HIPPA waiver of Authorization and waiver or alteration of informed consent process to identify potential participants for this research study. This study will be conducted in the context of the POSH clinic and will only include patients who participate in the POSH clinic. Identification of POSH patients: patients scheduled to be seen in general surgery clinic will be screened for candidacy for a POSH referral through CPRS. Specific referral criteria are based on established risk factors for post-operative complications and include age ≥ 60, multiple comorbid conditions, falls, mobility limitation or documented functional impairment. In addition to an alert being sent to the surgical team, a notice will be sent to the PCP, with information about the program and an invitation to contact the program manager with any questions or additional information. Patients will receive a single appointment to see the POSH team.

Once patients are referred to the POSH clinic, the POSH clinic coordinator, will contact the study staff. At that time, a chart review will be conducted to assess initial eligibility (abdominal surgery, surgery date is at least two weeks after to POSH clinic visit). Potential participants identified will then be sent an introductory letter signed by the PI that describes the study and informs them that they will be called regarding participation. In the letter, potential participants will be given an “opt-out” number to call in order to decline participation and/or further contact regarding participation. Five business days after the mailing, Veterans who have not called the study number to decline participation will be called by a study staff member to request their participation in the research study (see telephone screen script). In the telephone contact, the study staff member will inform the Veteran that he/she was selected for recruitment because he/she is an older Veteran who is been seen at the POSH Clinic and is having abdominal surgery and may be at nutritional risk.

Any Veteran who contacts or is contacted by study staff will be told that their participation is voluntary, and they may choose not to answer any questions that they find too sensitive. Also, Veterans will be told that their participation will not affect their care at the VA. The study staff member will explain the study in detail, including compensation. No study procedures will begin until formal, written informed consent has been obtained.

Consent Process

On the day of their POSH clinic visit, potential participants identified we will be informed again that he or she is being recruited because he/she is having abdominal elective surgery and is a patient in the POSH clinic. The participant will be told that their participation is voluntary, and they may choose not to answer any questions that they find too sensitive. Also, Veterans will be told that their participation will not affect their care at the VA. The study staff member will explain the study in detail. The participant will be will be given as long as they need to read through the consent form and HIPAA Authorization. Study staff will answer all questions and concerns. No study procedures will begin until formal, written informed consent has been obtained.

Study Interventions

Caloric Intake and Monitoring Protocol for Both Arms: Caloric needs will be prescribed for each participant using an established standard of 30 to 35 kcal/kg[41] at the VAPOSH clinic. To assure adequacy for all enrollees, calculated protein needs will be higher than the recommended 0.8 g/kg of body weight for both arms, **PoshControl** protein prescription = **1.0 g/kg of bodyweight** and **PeriHab** protein prescription = **1.6 g/kg of bodyweight**. Participants will be monitored by weekly phone calls during which study staff will ask the participant to recall their intake from the day before (24-hour dietary recall). This information will be used to ensure that both arms are meeting their calorie needs. If a participant in either arm has an inadequate intake they will be counseled on how to increase their current intake. Based on our previous assessment of similar populations, it is unlikely that the **PeriHab** arm will be able to meet the 1.6 g/kg of body weight protein prescription on their own and for that reason we are providing protein supplement to be consumed 3 times a day (as described below). The **PoshControl** arm will be given one ONS to consume every day prior to surgery.

PeriHab Arm Protein Perihabilitation Protocol: The protein supplementation protocol provides for three daily supplements of 30 g of high quality protein in the form of a liquid nutritional supplement (30 g). Subjects will receive sample menus to help the participants incorporate the increased protein into their daily intake. Individually packaged portions of the liquid supplement will be supplied at the VAPOSH clinic visit (T1). Participants will be given a two-week supply of supplement. Included will be a printed check-off sheet for participants to record protein supplement use. The protein check-off sheet, three-day food record, Actigraph log, and lids from the protein drink will be turned in on the day of surgery (T2). Following their surgery, participants will be given an additional four week supply of the same supplement at discharge and the same materials as at the VAPOSH clinic visit (T1). The protein check-off sheet, three-day food record, Actigraph log, and lids from the protein bottles will be turned in at the follow-up appointment (T3).

Participants will be contacted weekly by study staff and queried with a standard set of open-ended questions designed to identify problems with compliance. Participants who are having difficulty will be provided additional counseling to ensure they are able to achieve 30 grams of high quality protein three times a day.

PoshControl Arm Protocol: Participants in the PeriControl arm will be asked to consume 1 ONS protein supplement per day prior to surgery. They will be provided education on the role of nutrition to prepare for and heal from surgery with the following main messages, 1) complications associated with malnutrition; 2) the benefits of good nutrition; 3) tips for dietary intake when not hungry; 4) easy food preparation; and 5) what to eat. The study Registered Dietitian will instruct the participant to follow the information on the handout. Study staff will call the PoshControl arm participants once a week to identify problems with compliance,

answer any questions and also remind participant to complete their 3-day food records. The ONS check-off sheet, three-day food record, and lids from the Ensure Plus bottles will be turned in on the day of surgery (T2). Four weeks following surgery, PoshControl participants will return for a follow-up appointment and will bring Ensure Plus checklist, three-day food record, and Actigraph log.

Adverse Events

Given the study population of older Veterans undergoing surgery we anticipate adverse events that are not related to the study, including ER readmission following surgery, poor would healing, and surgical complications. Perioperative nutrition intervention should enhance rather than jeopardize the health status, and potential serious adverse events (SAE) for participants in this project are not expected. Regardless, we will minimize potential risk by careful screening of potential participants. All adverse events will be reported per Durham VAMC requirements. All Serious, Unanticipated and Related adverse events will be reported to IRB within 5 business days of hearing of the event. All other adverse events will be reported at continuing review.

Costs and/or Payments to Subjects

Study participants in both arms may receive up to $160 for full participation in the study. This payment information is provided in the informed consent document. Participants will receive $40.00 for time points 1 and 2, since these are times in which they would be coming to the VA for their preoperative care and surgery. They will receive $80.00 for time point 3.

Data and Safety Monitoring

The individuals responsible for data safety and monitoring will be the PI, the Registered Dietitian, project coordinator, and the study Co-Investigators.

Further data safety and monitoring will be provided by the PI. There will be several ongoing mechanisms for monitoring and reporting of adverse events: 1) ongoing participant contact via study personnel, 2) study telephone number provided to participants to report concerns related to study participation; and 3) weekly meetings between the PI and study personnel.

The PI will meet at least weekly with study personnel to discuss participants' reactions to outcome measures and assessments, weekly telephone calls, and any adverse events or unanticipated problems. Monthly meetings between the investigators and the project coordinator will allow for ongoing progress reports, including the number of participants currently involved in the study and scheduled data collection from participants, as well as notification and review of any AEs. Safety monitoring for adverse events (AEs) will be conducted in real time by the PI and/or project coordinator. The following information about adverse events will be collected: 1) the onset and resolution of the AE, 2) an assessment of the severity or intensity (use existing grading scales whenever possible), 3) an assessment of the relationship of the event to the study (definitely, probably, possibly or not related), and 4) action taken (e.g., none, referral to physician, start or increase concomitant medication). The PI will determine the severity of the event, will assign attribution to the event, and will monitor the event until its resolution. All adverse events will be reported per Durham VAMC requirements. All Serious, Unanticipated and Related adverse events will be reported to IRB within 5 business days of hearing of the event. All other adverse events will be reported at continuing review.

Withdrawal of Participants

Subjects who do not have surgery will be withdrawn from the study. Additionally, if a subject has to have emergency surgery, rather than elective surgery during the two weeks between the POSH clinic visit and their scheduled surgery date they will be withdrawn from the study. Finally, subjects who refuse to consume protein supplement will be withdrawn from the study.

If a participant decides to withdraw from the study, they will be instructed to contact the PI and discuss the reason for withdraw. This information will be documented to help better understand the reasons that the participant was unable to complete the study.

Data Analysis and Statistical Considerations

Data management and quality control: We will employ REDCap (Research Electronic Data Capture) for data entry. Key components of this activity include data entry screen programming and database testing and validation. The database will include study default parameters and ranges for database, protocols, users, and access rights. Access and data entry to the database will be controlled by login permissions, and the database will be backed up daily, with full backups occurring weekly, and quarterly backups retained for perpetuity. The database will be routinely checked for data integrity and quality. In addition, since some data will require direct download from computerized databases (e.g. VA patient information, lab findings) a final relational database will be built to be used for analysis in SAS, combining data from all data sources. This process will include quality control, developing an appropriate query, validation, and justification procedures, auditing, developing a manual of procedures and documentation, interim reporting of data flow, and maintaining security and patient confidentiality of the data base. The analysis database derived from this source data will be de-identified. Identifying information will be viewed and managed only by the data manager and appropriately consented data collection staff.

Quality control procedures will be established for each component of the study. At each level of data management, and for each subject contact, strict adherence to VHA policy will be observed regarding HIPAA, IRB and other VHA patient quality controls. These procedures include not identifying any patient or provider on any of the reports generated from this study. All computer files will be password protected. Files containing names and addresses will have a separate password, will be accessible only to personnel who need to contact the subjects, and will be stored separately. Ultimately, a de-identified file appropriate for analysis will be produced for report generation and analysis. All analysis and Data management personnel are current with all VA mandated security training.

Aim 2.1 Analysis Plan:

Feasibility proportions for future screening and recruitment will be calculated at the end of the intervention using the following:

1. Proportion of patients recruited will be calculated as the number of patients deemed potentially eligible and contacted for enrollment divided by the total number of patients enrolled.
    - Feasibility Hypothesis: $\geq$75% of patients approached for recruitment will agree to participate

Fidelity proportions will be calculated for adherence and retention at the end of the intervention using the following:

1. Proportion adherent to nutrition intervention will be computed by the number of empty supplement containers divided by the number of possible supplement containers that could be consumed.

2. Proportion adherent to nutrition intervention will also be computed by the number of meals consumed that are 25 grams of protein divided by the number of possible meals that could be achieved. For the PoshControl arm, adherence will be assessed by the number of dietary changes they make based on the educational handout provided to them at baseline. These will be determined by using diet records for 3 days prior to surgery and 3 days following surgery. Diet food records are valid method for collecting dietary intake data and have been administered in Veteran populations.[42] We have experience administering and analyzing this data.[1]
    - Adherence Hypothesis: ≥75% of the time PeriHab participants will adhere to the intervention and ≥75% of the time controls will show at least one recommended dietary change in their 3-day diet record
3. Proportion retention will be computed by dividing the number of retained subjects at the end of the intervention by the total number randomized into the study.
    - Retention Hypothesis: ≥80% of participants will remain in the study for the duration of the trial

We will calculate these rates of retention and adherence and their respective confidence intervals overall and by group. While non-powerful, we will assess if these rates differ by chi-square test of proportion and Poisson regression respectively. In a series of sensitivity tests, we will assess if adherence overall was impacted by demographic or symptomatic variables (such as chronic health conditions, living arrangements, surgery, functional status, and nutrition status).

Acceptability will be assessed by:

1. Calculating levels of attrition.
    - Patient satisfaction will be assessed by a brief 5-item questionnaire: a) satisfaction with participating in the study; b) satisfaction with directions on how and when to consume the protein supplement, c) satisfaction of the taste of the protein supplement, d) satisfaction with functional status after protein e) satisfaction with interactions with the registered dietitian. ≥80% of participants will report satisfaction with participating in the study.
2. Qualitative semi-structured interviews in a subset of the participants. A qualitative analytical approach is well suited to exploring concepts related to a complex process (malnutrition and nutrition intervention). We anticipate we will achieve thematic saturation by enrolling 20 participants. The data in the interview transcripts will be coded using Atlas software. Perform the analysis using the skills obtained in my proposed coursework and with the assistance from my co-investigators. Data analysis will include summarizing the major topics of discussion, synthesizing recurring themes, and selecting exemplars of these themes from individual comments. In concert with the quantitative results, these data will be used to inform the design of a larger trial aimed at improving outcomes for older, malnourished Veterans.
    - Patients will be selected using maximum variation purposive sampling including to include a mix of ages, genders, races, surgical procedures, and nutrition status.
    - Each semi-structure interview will be conducted at the endpoint visit and will last approximately 15 minutes. The interviews will be conducted according to a script developed in close collaboration with my co-investigators.
    - All interviews will be tape-recorded and transcribed. The interviewer will also take written notes to capture changes in emotion or enthusiasm related to the response to each question that will not be captured in transcribed reports.

Aim 1.2 Analysis Plan: This design is a two-armed clinical trial, with replicate measures at three time points: baseline, two, and six weeks. Since subjects are randomized to either PeriHab or PoshControl arm, and the groups are presumed equal at baseline, the analysis is straightforward. Following the Good Clinical Practice Guidelines for the analysis of a clinical trial, we will employ mixed models,[43] analyze under an Intent to Treat (ITT) criteria, and control for baseline and assess the impact of Time, Treatment Group and the interaction of these variables on the outcomes. Relative to the usual repeated measures designs, mixed models have several advantages: 1) missing values present no particular difficulties in estimation and the estimates are unbiased as long as the set of variables leading to MAR are estimated, 2) the usual assumption of conditional independence (compound symmetry) used in standard repeated measures need not be made, and 3) the actual times of measurement need not be equivalent across subjects. Controlling for the individual baseline values for the particular outcomes, the trajectories over time and differences in those trajectories will be assessed. Following the statistical principles section from the International Conference on Harmonization, we will select covariates (e.g., age, race, number of comorbidities) for the primary models a priori, but we also will conduct auxiliary sensitivity analyses that evaluate whether potential group imbalances bias the treatment effect estimate. These analyses will be performed using conventional testing for confounding.

For any particular outcome, the general form of the model will be:

$Y_{it} = \beta 0 + \beta\ 1(\text{group}) + \beta\ 2(\text{time}_t) + \beta\ 3(\text{group}*\text{time}_t) + \beta\ 4(\text{covariates}) + \varepsilon_{it}$

Where i is an indicator of person, and time is defined as t=1, 2 (measuring week 2 or 6), and the β's are regression coefficients connecting the predictors to the outcome. For brevity, we list β4 as a vector of K regression coefficients linking the K covariates to the outcome. As defined, the overall test of the intervention effect will be the joint effect of group and group*time on 2 df (β1 and β2) assessing an overall effect of group, and if this group effect is constant over time. If significant, follow-up tests will assess where group differences lie. In particular, we note that if the time by group interaction is rejected, we will test if the groups differ at the end of 6 weeks (a test of effect at the completion of the intervention).

We will carefully examine model assumptions, including the distribution of model residuals, additively, linearity, and influential observations, and will, if necessary, re-parameterize the models or transform the outcomes accordingly.

We note that we have listed numerous measures to be analyzed as outcomes, but have listed only 2 domains of outcomes as primary (physical function and a biological index of nutrition status and inflammation). We will not adjust for Type-I error rate for these primary outcomes. Rather, we will warn the reader of the multiple outcomes tested and the chance for a Type-I error.

Secondary Outcomes: At the conclusion of the study, we will have a rich database with which to conduct follow-up exploratory analyses. We will perform multiple exploratory analyses of the remaining measures. In addition to the impact of the intervention on the secondary outcomes, we will assess mediation of the group effect on the primary outcome by demographic, comorbid and adherence variables. Subjects may differ in their process of change depending on baseline demographic and functional status values. Second, we will assess the functional form of the change over time, by looking at non-linear functions of change. For example, change in function and performance is likely to be non-linear, initially changing quickly and leveling at points distal from baseline. It would be important to note if this change differed by group. Finally, we will assess whether the trajectories of change, irrespective of group assignment, are similar for individuals. In this application, we have listed several variables, which we expect to change as result of the intervention. We further hypothesize that all these variables will change in the same pattern. To test this hypothesis, across the

range of outcome measures, we can look at overall change through the use of multivariate tests (Bock[44] or Anderson[45]) for the singly measured functional items, and by assessment of correlated trajectories for those outcomes measured repeatedly. With appropriate weighting for number of observations per individuals, the correlation between individual trajectories can assessed. A positive correlation between the trajectories for any two outcomes will indicate that the subjects changed similarly for the 2 outcomes, and will provide additional support for the notion that the intervention had a generalized effect across the outcomes. Significant correlations would perhaps indicate mechanistic/causal linkage between variables over time, or, from a reliability standpoint, may indicate that the subsequent trial may want to employ summary measures aggregating across outcome measures, or, alternatively, employ multivariate tests across several outcomes to assess the group differences, reducing the chance of Type-I error inherent in the testing of multiple variables.

The results of these analyses will provide invaluable information regarding the process and functional forms and, potentially, the causal pathways of the intervention process. For example, one important analysis will enter 'level of compliance to the intervention' into the analysis, allowing for a 'per protocol' analysis of the results.

Power Estimate: Estimate effect sizes for the physical function between-group comparisons and the power available to detect effect with two-tailed tests are provided below for the total N= 80. The objective of this pilot study is to perform preliminary evaluation of a nutrition perihabilitation program in malnourished Veterans, in preparation for a larger grant submission. This pilot work will allow us to conduct sample size, effect sizes, and power analyses for a larger clinical trial. To date, no randomized controlled nutrition perihabilitation study has been conducted in malnourished Veterans. As such, we turned to the literature. Gillis et al.,[46] reported that older adults undergoing colorectal resectioning surgery who were given nutrition supplementation 3 weeks before surgery improved by 23.7 meters on the 6 minute walk test while the arm given nutrition supplement following the surgery declined by -21.3 meters. The pooled standard deviation of these changes was 67.75. Thus, a standard difference of 0.66 = (23.7 - (-21.3))/67.75 was observed. Differences of this magnitude have been labeled as ‘medium’ in the statistical power literature (70). Assuming a standard deviation in the change scores of 67.75, n=40 per group, power=80% and alpha=0.05 (two-tailed), we are powered to detect a difference in changes scores of a standardized magnitude of 0.634, in line with the results of Gillis et al.[46]

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