TITLE: Personalized Targeted Nutrition via StructurEd Nutrition Delivery Pathway to Improve Resilience in Older Adult Trauma Patients – SeND Home

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SPECIFIC AIMS AND SCIENTIFIC JUSTIFICATION: *Extensive data demonstrates trauma patients experience significant post-hospital impairments in physical function, muscle wasting/weakness, poor quality of life (QoL), decreased resilience, and impaired return to everyday life.*[1-3] Resilience in older adult trauma patients would include improved QoL, physical function, and the ability to return home. Intensive Care Unit-Acquired Weakness (ICU-AW) burden survivors for months to years.[1] Post-ICU data consistently shows functional limitations resulting in only 50% of patients returning to employment, difficulty performing activities of daily living, and only 60-65% reaching functional exercise capacity at 1 year.[8] Major national ICU/trauma trials groups emphasize declining mortality rates in Trauma/ICU patients that future trials need to focus on functional QoL as a primary endpoint[4]. A significant driver for weakness is trauma and critical illness leading to a catabolic state immediately following injury and persisting throughout hospital stay[5]. Specifically, this acute catabolic response leads to severe muscle mass loss and impaired muscle function.[1,3,6] These injuries and acute catabolic response predispose patients to a high risk of malnutrition, and additionally, the risk of complications is significantly increased once malnutrition ensues[7]. In trauma, malnutrition correlates with poor outcomes, including higher mortality, complications, and chronic illness, contributing to higher healthcare costs.[8,9]

Older adults account for an increasingly large proportion of patients presenting for trauma care, and 62% either present with or are at risk for malnutrition at hospital admission.[10,11] Following admission, malnutrition is further exacerbated as these patients' are routinely classified as "nothing by mouth" (NPO) due to physiologic complications or the need to undergo repeated procedures. Moreover, ICU stays are associated with significant underfeeding (~50% of predicted), while post-ICU care often reveals an unrecognized hypermetabolic state with even poorer nutrition delivery. The impact of malnutrition on older adult trauma patient outcomes is profound, increasing morbidity, reducing the likelihood of discharge home, and increasing mortality six-fold.[12-14] By contrast, it is well-known that effective, goal-directed nutrition improves outcomes and resilience in ICU patients.[5]

Little is known about why post-ICU and post-hospitalization nutrition is poor among older adult trauma patients. One area that has consistently failed to be addressed in trauma nutrition research is the post-ICU period. This period is more extended than the patient's ICU stay, and data shows the patient's caloric requirements increase post-ICU significantly as the body attempts to recover.[15,16] However, data also indicates that patients routinely fail to achieve nutritional needs when they need the nutrition most to regain physical function.[17]

It is unclear why hospitals cannot provide or deliver adequate nutrition to older adults. One study revealed a post-ICU oral calorie intake of only 700kcal/day, and patients consumed<50% of calorie/protein needs. When post-ICU oral intake was provided alone without high-protein oral nutrition supplements, only 37% of energy and 48% of protein requirements were met.[18] We have shown that early oral nutrition supplements alone improve the length of stay by 2 days in malnourished trauma patients, yet, **only 1.9%** received them.[19] Despite these findings, there is no consensus on the optimal approach to screen for, measure, and address malnutrition among hospitalized critically ill older adults. There remains a **critical need** to improve the approach to managing malnutrition in older adults following trauma, which will improve outcomes, resilience, and QoL for these patients.

*To address this **clinical care gap**, we have developed a comprehensive, multidimensional nutrition delivery program for older adult trauma patients: Structured Nutrition Delivery (SeND Home).* The SeND Home program consists of a multidisciplinary team of RDs, PTs, pharmacists, nurses, and providers and is designed to optimize both in-hospital and post-hospital care for older adult trauma patients. The structure of SeND Home is based on diagnostic and treatment interventions developed in our LEEP-COVID trial (NCT04350073) for optimizing nutrition delivery in critically ill COVID-19 patients,[20,21] as well as international ICU nutrition guidelines to determine caloric needs.[22]

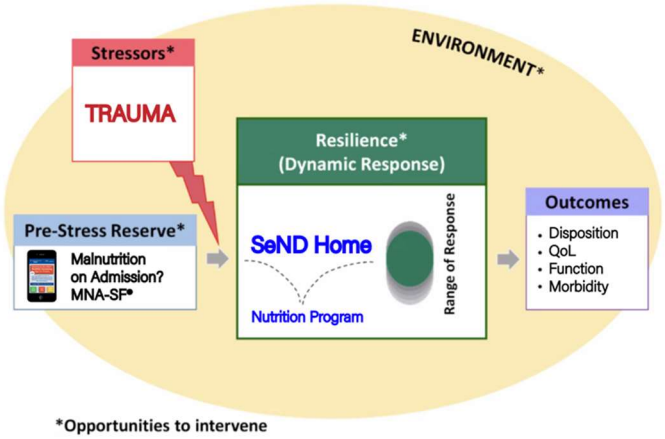


Figure 1. Overview of the SeND Home Pathway

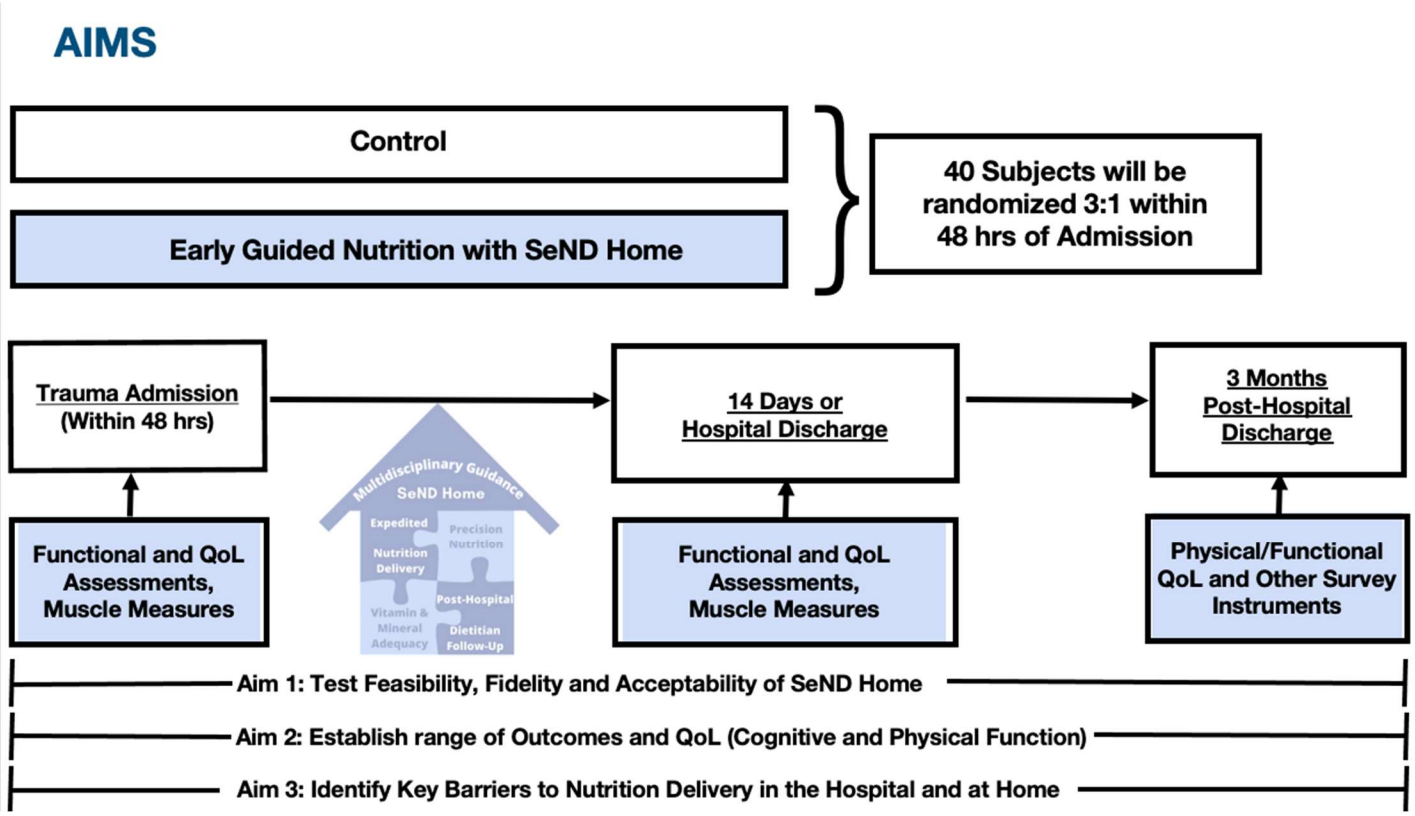
Our *long-term goal* is to improve resilience for critically ill older adults who suffer trauma **(Figure 1**). The *overall objective* of the current proposal is to fully develop the SeND Home program through a formal feasibility, acceptability, and fidelity trial using an iterative design. We will accomplish our goals through the following aims:

Aim 1: Assess the feasibility, fidelity, and acceptability of SeND Home for older adult trauma patients. We will enroll 40 older patients and follow them post-discharge using SeND Home using a 3:1 randomization plan. We will determine feasibility by measuring the ability to recruit and enroll the target number of patients, maintain 90% enrollment over a three-month period, and adherence rates to the study protocol. We will test acceptability by interviewing patients and stakeholders. We determine fidelity by measuring the proportion of inventions delivered according to the study protocol.

Aim 2: Establish a plausible range of nutrition related outcomes for patients participating in SeND Home. We will assess how outcomes are operationalized in both the intervention and control arm and reflect change relevant to planning an RCT, using the following measures (self-reported health[23], PROMIS, Brief Resilience Scale (BRS), sarcopenia index[24,25], simple clinical symptom index (SARC-F),[26-29] change in muscle mass[30], physical function measures[31] (Table 1), cognitive function, complications, and healthcare utilization.

Aim 3: Identify key barriers to nutrition delivery for older adult trauma patients in the hospital and discharge setting. We will conduct a qualitative descriptive study using in-depth interviews to explore the understanding of and barriers to meeting nutritional needs among a diverse group of older adult trauma patients who tolerate oral nutrition. We will also explore social norms/community influence, psychosocial functioning, accessibility, and financial functioning. We will conduct interviews until we reach meaning saturation, which we anticipate around 16 interviews. This design will allow for a rich exploration of the lived experience of this unique population, in their words, which is critical for understanding what quantitative measures are optimal for future work.

This program will allow for precise nutrition delivery from the hospital to the home setting that does not exist and is urgently needed to fill a substantial gap in promoting recovery of older adult trauma patients. A key component is goal-directed oral nutrition throughout the hospital stay, including providing ONS to ensure adequate intake.



DESIGN AND METHODS: This is a Pilot study designed to set up for an RCT comparing the SeND Home pathway to a standard of care nutrition delivery in critically ill older adult trauma patients. The SeND Home Pathway supports patients from hospital admission to 4-weeks post-hospital discharge, providing a comprehensive and personalized plan of care carried to completion as summarized in **Figure 2**. Upon meeting

inclusion/exclusion criteria, 40 patients will be randomized into the intervention or standard of care control group, respectively. The total duration of the study will be 2 years.

POPULATION: This is a pilot study of all older adult trauma patients without traumatic brain injury expected to survive their admission. *Inclusion: O*lder adult patients admitted to the trauma service; *Exclusion:* Expected withdrawal of life-sustaining treatment within 48 hours; Prisoners.

RECRUITMENT: *Screening:* The screening form is used to evaluate the trauma service patients daily for eligibility.

Potentially eligible participants will be identified, and a review of the medical record and/or contact with the trauma team to determine if they qualify. We will use a stratified purposive sampling procedure similar to that Dr. Cox has utilized in multiple ICU-based projects to ensure the recruitment of a representative cohort that is diverse in race, ethnicity, gender, and insurance. Participants will be met in person by our research team with a track record of enrolling older adult trauma patients to discuss the intervention and consent for this study. In our LEEP-COVID ICU study, and we were able to recruit 58 ICU subjects using these methods.

*INTERVENTION***:** *Overview of In-Hospital Intervention:* Beginning in the hospital, the SeND Home program will expedite nutritional support by 1) Defining personalized longitudinal caloric requirements starting at 72 hours post-admission using indirect calorimetry (IC) regularly throughout the hospital course allowing precision nutrition delivery; 2) Identifying protein-calorie malnutrition using dietitian exam and the Mini Nutritional Assessment Short-Form (MNA®-SF)[32] and effects of nutrition delivery via standardized methods, including a) functional measures will be assessed by hospital-based PTs, b) muscle mass, intramuscular adipose tissue and muscle glycogen stores (MuscleSound muscle-specific ultrasound), c) body composition (via Bioimpedance Analysis (BIA)), and 3) Accelerating optimized nutrition delivery by initiating early targeted nutrition. Once a patient passes for a full liquid diet, supplements will be provided, optimizing protein, calorie, vitamin, and mineral intake until RD follow-up assessment. PT will evaluate for strength and exercise recommendations.

Overview of Post-Hospital Nutrition Supplementation and Discharge Follow-Up: SeND Home includes regular follow-up by RDs over 3-months to discuss post-hospital nutrition management, promote optimal recovery, and provide resources such as educational handouts and personalized nutrition goals. After discharge, patients will be given 4-weeks of oral supplements to promote intake. Two and four weeks post-hospital discharge, patients will receive a follow-up call from an RD to discuss nutrition and provide resources and recommendations. Patients will be asked to return for a 3 month follow-up visit to complete surveys and assessments.

Send Home Pathway Nutrition Energy Goal Measurements Via Indirect Calorimetry (IC) and Nitrogen Measures: To determine presenting and change in Energy Expenditure starting at 72 hours post hospital admission, both the Q-NRG IC and urine nitrogen balance measures will be used to guide nutrition goals. Q-NRG is a next-generation metabolic cart to determine energy expenditure, VO2, VCO2, and the respiratory quotient, which will be used to guide nutrition goals. We will conduct metabolic cart measurements every 3 days (+/- 2 days) in ICU and every 7 days (+/- 2 days) in the post-ICU period and nitrogen balance will be done 24 hours prior to IC when possible.. SCCM/ASPEN33 nutrition guidelines guide other nutrition management not covered by study algorithms.

Protein Provision Guidelines: The minimum protein delivery in the SeND Home Arm is 1.2 g/kg actual weight for BMI<35 and 2-2.5 g/kg for BMI>35[33]. Adjustments may be made based on IC measurements. It is anticipated that our patients may require additional protein, based upon the patient's calculated nutritional requirements for their condition per SCCM/ASPEN nutrition guidelines[33], true targeted nutrition delivery will be achieved in the SeND Home group via targeted tolerance criteria to allow standardized adjustment of nutrition components.

*RANDOMIZATION***:** Following confirmation of inclusion/exclusion criteria and informed consent by the patient, the patient will be randomized 3:1 to either SeND Home precision nutrition pathway or control arm All those randomized will be included in data analysis in accordance with intent-to-treat study principles.

*MEASURES***:** ***Aim 1:*** **Feasibility** will be tested by determining the number of patients recruited per unit time, the number of study patients who adhere to the SeND Home treatment protocol, and the percentage of patients we are able to retain to study completion. Additionally, we will measure participant burden, including the time taken to complete each outcome and how well they are tolerated, duration of testing time, and patient ability to successfully complete testing in one cycle will be recorded. To test **Acceptability**, we will interview providers and patients as we enroll, and we will iteratively adapt the SeND home design as progress throughout the study.

Specifically, providers, PTs, RDs will undergo measures of satisfaction and usefulness following every 5 patients enrolled in SeND Home to adapt the pathway developing an intervention useful for improving nutrition guidance, goals, and outcomes for older adult trauma patients. Finally, to test the **Fidelity** of SeND Home, we will determine the number of interventions delivered per protocol in the ICU, on the floor, and in-home.

Aim 2: *Muscle and Body Composition: Physical Function Measures* will cover both upper and lower body strength and endurance.[34-52] Despite the notion that these tests would not normally be feasible in a medical ICU, older adult trauma patients in a surgical ICU are admitted following falls 90% of the time, are fully functional at baseline prior to admission, and the highest reason for admission to the Duke SICU is close respiratory monitoring for rib fractures. Additionally, **these functional measures are feasible and currently being performed successfully in our SICU** as part of our LEEP-COVID trial mentioned above and early TPN nutrition trial on patients with severe abdominal injuries. In addition to the above staff administered assessments, patient reports will be completed by the patient with study staff. Finally, we will use our same LEEP-COVID protocols to evaluate patients using MuscleSound and BIA. MuscleSound (muscle-specific ultrasound provided without cost) will rapidly and non-invasively evaluate intramuscular glycogen content (IMGC), intramuscular adipose tissue (IMAT), muscle thickness, and volume in the rectus femoris, vastus lateralis, and intercostal/pectoralis.[49-51]. Additionally, we have demonstrated associations between glycogen deficiency and cachexia[53], suggesting this approach may help evaluate nutritional and muscle status. MuscleSound will be complemented by body composition measurements via advanced bioimpedance measures[52] using a bioimpedance analysis (BIA) device (Inbody S10), which utilizes hand-to-foot BIA that sends varying frequencies of alternating current through the body. These impedance values are then used to predict segmental (arm, leg, and truck) fat mass, fat-free mass, lean body mass, muscle mass, intracellular, extracellular, and total body water. We will also collect baseline demographics, ICU severity, and Physical Therapy Scores from the chart at enrollment, and we will continue to collect physical therapy and CAM-ICU scores.

Aim 3: We will conduct a qualitative descriptive study[54,55] using in-depth interviews (IDIs). We will aim to enroll a purposefully selected,[56] diverse study population (e.g., race, ethnicity, and gender) of older adult trauma patients who tolerate oral nutrition and are identified during their hospital course. We will conduct the telephone, zoom, or in-person IDIs until we reach meaning saturation[57], which research has demonstrated can be reached by 16 interviews. We will conduct up to 20 interviews if we determine additional information is needed to reach saturation; fewer interviews may also be conducted if meaning saturation is reached before 16 interviews. During the IDIs, we will explore the understanding of and barriers to meeting nutritional needs. We will also explore social norms/community influence, psychosocial functioning, accessibility, and financial functioning. IDIs will be conducted by trained QualCore qualitative interviews and audio-recorded with participant's permission.

*ANALYSIS***:** Given the magnitude and costs of a more extensive definitive randomized controlled trial study, we feel justified in proceeding with a pilot trial wherein we will enroll patients to evaluate the specific study aims. This is a pilot study measuring feasibility, acceptability, and fidelity.

We will be enrolling 40 patients and subsequently following them post-discharge using SeND Home using a 3:1 randomization plan. A sample size of 40 should be enough observations to provide useful information about the measures of feasibility. Feasibility will be tested by determining recruitment per unit time, protocol adherence, the percent retention to study completion, participant burden, duration of testing time, patient ability to successfully complete testing in one cycle. To test Acceptability, we will interview providers and patients, and we will iteratively adapt SeND Home throughout the study following satisfaction measures. Finally, we will determine the number of interventions delivered per protocol to test Fidelity. Analysis of initial malnutrition status (malnutrition vs. no malnutrition, MNA-SF) will be examined using chi-squared tests for categorical variables (gender, ethnicity) and using Z-test or Wilcoxon tests for continuous variables depending on whether the variables are normally or non-normally distributed, respectively. The analysis will be similar for sarcopenia.

*Interviews/Qualitative Data Analysis***:** To monitor for meaning saturation, interviewers will document the key findings in debriefing forms after each IDI. After the 12th IDI, the debriefing forms will be reviewed to determine if meaning saturation has been achieved for the main domains (i.e., when interviewers/investigators believe that no further clinically meaningful insights will be identified in additional IDIs). Data will be continually monitored after sets of two interviews, until meaning saturation is reached or 20 IDIs are conducted. We will use applied thematic analysis to formally analyze the data.[58] Following a transcription protocol [59], audio recordings will be transcribed verbatim without identifiers. Two QualCore analysts and I will use NVivo [60] qualitative analysis software to develop and apply structural (a priori) codes to segment participants' narratives into conceptual

categories (e.g., all text describing a similar concept). Analysts will then identify and apply content-driven (emergent) codes to the text for each of the conceptual categories (e.g., potential themes). Inter-coder reliability assessments will be conducted on 25% of transcripts. Discrepancies in coding will be resolved through analyst discussions; transcripts will be re-coded, and the codebook revised accordingly. Once coding is complete, we will examine code frequencies across transcripts to identify salient factors for patients, followed by comparing and contrasting factors as needed. Analytical memos will be written describing the factors influencing patient nutrition perceptions following trauma, together with illustrative quotes. The findings will be used to identify the optimal quantitative measures to use in future research.

FUTURE FUNDING: The results of this work will provide an innovative pathway, SeND Home, to improve nutrition and overall outcomes, helping older adult trauma patients bounce back from a major stressor. Upon completion of the development of SeND Home, we will submit a randomized controlled trial using SeND Home via an R01 mechanism at the National Institute on Aging.

RELEVANCE TO OAIC: Reserve and resilience are known qualities that promote positive outcomes in older adult patients. However, very few studies have examined these qualities as they relate to the short and long-term experience of trauma in these patients. Trauma is one of the most common late-life stressors older adults must endure, and early measures to promote recovery in these patients will improve overall outcomes. Using the OAIC Analysis Core to help with RedCap and analysis and Health and Mobility Measures Core for educating and assisting with performing functional measures, this project will provide a better platform to care for these patients and what factors lead to resiliency and disposition home fitting within the OAIC mission.

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