

# Medically-Tailored Meals to Prevent Recurrent Hepatic Encephalopathy: The BRAINFOOD Pilot Trial

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**Medically-Tailored Meals to Prevent Recurrent Hepatic Encephalopathy: The BRAINFOOD Pilot Trial**

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## SUMMARY

Study Name	Medically-Tailored Meals to Prevent Recurrent Hepatic Encephalopathy: The BRAINFOOD Pilot trial
Subject Population	<u>Stage 1:</u> At least 30 patients with cirrhosis including 10 with compensated cirrhosis, 10 with moderate to severe ascites and 10 with a history of overt hepatic encephalopathy (HE) <u>Stage 2:</u> At least 20 patients with cirrhosis and a recent history of overt HE
Objective	To determine the feasibility of a trial that uses medically-tailored meals (MTM) as an intervention in persons with a history of HE
Design	Two-stage feasibility trial
Stages	<u>Stage 1:</u> Feasibility of assessments <u>Stage 2:</u> Pre-Post trial after refining selection of assessments based on patient ability to complete and detect changes
Procedures	<ul style="list-style-type: none"> <li>- Stage 1 &amp; Stage 2: Screen for patients with cirrhosis and recent episode of overt HE and/or ascites.</li> <li>- Consent eligible patients.</li> <li>- <u>Stage 1:</u> Feasibility of assessments <ul style="list-style-type: none"> <li>• Complete baseline assessments in-person</li> <li>• Subjects receive a nutrition education hand-out and 2 weeks of MTM. They undergo 24-hour dietary recalls during this intervention phase.</li> <li>• Subjects complete final study visit at 4±1 weeks in-person and complete all assessments</li> </ul> </li> <li>- <u>Stage 2:</u> Pre-Post trial after refining selection of assessments based on patient ability to complete and detect changes from Stage 1. <ul style="list-style-type: none"> <li>• After enrollment, there is a 4±1 run-in phase to demonstrate interest</li> <li>• Subjects return for in-person visit to complete baseline assessments</li> <li>• Subjects receive a nutrition education hand-out and 6 weeks of MTM. They undergo 24-hour dietary recalls during this intervention phase.</li> <li>• Subjects return for in person visit at 11±2 weeks and complete all assessments. There is a 12-week observational period.</li> <li>• Subjects complete final study visit at 24±3 weeks via phone.</li> </ul> </li> </ul>
Primary Outcomes	<ol style="list-style-type: none"> <li>1. Overall subject retention rate, defined as subjects who complete all study visits (Stage 1 &amp; Stage 2).</li> <li>2. Subject adherence rate to MTM intervention (Stage 2 only).</li> </ol>
Secondary Outcomes	<ol style="list-style-type: none"> <li>1. Proportion of subjects who complete all study assessments and procedures.</li> <li>2. The time required to complete assessments (Stage 1 only).</li> <li>3. The number of eligible candidates screened and proportion of those enrolled.</li> <li>4. Subject drop-out rate.</li> </ol>
Exploratory Outcomes	<ol style="list-style-type: none"> <li>1. Determine if MTM improves the subject's nutritional intake (Stage 2 only).</li> <li>2. Determine if MTM affects the subject's cognitive function or health-related quality of life (HRQOL) (Stage 2 only).</li> <li>3. Explore whether MTM affects clinical outcomes and healthcare utilization rates (Stage 2 only).</li> <li>4. Patient satisfaction and preferences of MTM (Stage 2 only).</li> </ol>

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## SIGNIFICANCE

Cirrhosis is the final common pathway for all chronic liver diseases.(1) It is common, with a US prevalence >1 million and rising owing to age-related metabolic comorbidities.(2) Two-thirds of contemporary patients with cirrhosis are now  $\geq 60$  years old.(3) The mortality and healthcare costs associated with cirrhosis have nearly doubled within the last 10 years.(4, 5) More than any other factor, these adverse outcomes are driven by the development of hepatic encephalopathy (HE). A spectrum of reversible cognitive changes, HE ranges from inattention and executive function deficits to a severe form marked by lethargy, disorientation, and even coma.(3-6) Over 40% of patients with cirrhosis will develop HE.(6, 7) HE is associated with increased mortality, malnutrition, sarcopenia,(8) frailty,(9) debility,(10) falls,(11-13) and frequent hospitalization.(14)

HE is caused by brain exposure to ammonia, a waste product of bacterial metabolism in the gut. Normally the liver converts ammonia to urea. In cirrhosis, however, ammonia is distributed peripherally. Muscle is the main auxiliary site of ammonia clearance. Ammonia detoxification by muscle consumes branched-chain amino acids that are liberated in a catabolic process.(15) A vicious cycle emerges. **Hyperammonemia begets sarcopenia which, in turn, raises blood ammonia levels.**(16) Sarcopenia is present in  $\geq 50\%$  of patients with cirrhosis.(8) Contrary to the widely held myth that excess protein intake raises ammonia levels and HE risk, increased protein intake is safe in patients with cirrhosis including those with history of HE.(17) To reduce recurrent HE, patients are recommended to consume a high protein diet.(18)

Nutrition is a central component in management of cirrhosis complications. Guidelines recommend that patients with HE receive a high protein diet with 1.25 g/kg ideal body weight (roughly 1 g/kg actual body weight).(18) Protein supplementation has been shown to improve health related quality of life (HRQOL) and to reduce the risk of HE.(19, 20) Unfortunately, implementation of a high-protein diet is challenging. Food insecurity and poverty are highly prevalent among patients with cirrhosis.(21) Furthermore, most patients with cirrhosis, particularly those with ascites, report severe anorexia.(22)

One solution to the problem of malnutrition and therefore recurrent HE is to provide standardized meals for the short-term during the high-risk period after an HE episode. Medically-tailored meals (MTM) have been linked to reductions in expected readmissions and the incidence of falls for nutritionally at-risk elders.(23, 24) Low-sodium MTMs have been shown to be cost-effective and to improve quality of life in patients with hypertension.(25) In a recent randomized controlled trial, patients with acutely decompensated congestive heart failure were randomized to receive home-delivered low-salt meals or usual care.(26) This study demonstrated a substantial reduction in the risk of readmission.(27) We recently completed a 1:1 randomized trial of high-protein, low-sodium home-delivered meals versus standard of care (diet education) for 40 patients with refractory ascites (aged 60 on average).(NCT03493204) The meals improved need for paracentesis, quality of life, and physical function at a cost of \$500/person-month. We now turn our attention to the prevention of HE. The BRAINFOOD study proposes to determine whether home-delivered high protein MTM can reduce recurrent HE in patients with a recent episode of overt HE. Before proceeding with a large-scale trial, we will conduct a pilot feasibility trial.

## **1. STUDY OBJECTIVES**

The primary objective is to determine the feasibility of conducting a future definitive randomized-controlled trial of MTM in a study population with a history of overt HE. This feasibility trial will be conducted in two stages. Stage 1 will evaluate the feasibility of all assessment processes among three different populations of cirrhosis patients. The results of Stage 1 will be utilized to improve study processes and procedures of Stage 2 prior to the start of Stage 2 enrollment. Stage 2 will evaluate MTM intervention fidelity and adherence, determine recruitment and retention rates and determine efficacy of MTM among a pool of cirrhosis subjects with overt HE.

### **1.1 SPECIFIC AIMS**

#### **1.1.1 Primary Aims**

**Aim 1:** To determine the overall subject retention rate of Stage 1 and Stage 2.

**1a. Stage 1:** The proportion of subjects in each arm who complete all study visits from baseline to 4±1 week.

**1b. Stage 2:** The proportion of subjects who complete all study visits from baseline to 24±3 weeks.

**Aim 2:** To determine the MTM intervention adherence rate in Stage 2 as assessed using the 24-hour Diet Recall interview and/or the VioScreen FFQ.

**2a. Stage 2:** The proportion of subjects who consume ≥75% of delivered meals and evening snack from baseline to 9±2 weeks.

#### **1.1.2 Secondary Aims**

Secondary aims of this trial will include feasibility of study procedures:

**Aim 3:** To determine the proportion of subjects who complete all 24-hour Diet Recall interviews in Stage 1 and Stage 2.

**3a. Stage 1:** The proportion of subjects in each arm who complete the 24-hour Diet Recall between Study Days 9 and 17.

**3b. Stage 2:** The proportion of subjects who complete all four 24-hour Diet Recalls at baseline and 9 weeks.

**Aim 4:** To determine the proportion of subjects who complete all study procedures and assessments in Stage 1 and Stage 2.

**4a. Stage 1:** The proportion of subjects who complete all study procedures and assessments at baseline and Week 4±1 visit.

**4b. Stage 2:** The proportion of subjects who complete all study procedures and assessments at baseline, Week 11 and Week 24±3 visits.

**Aim 5:** To determine the time required for Stage 1 subjects to complete each study procedure at baseline and the Week 4±1 end of study visit.

**5a. Stage 1:** The time required, measured in minutes and seconds, for subjects to complete each individual assessment at baseline and Week 4±1, and the total time required to complete both study visits.

**Aim 6:** To determine the number of eligible candidates formally screened within 6 months of study start date, and the percentage of eligible candidates who were recruited and enrolled into Stage 1 and Stage 2.

**6a. Stage 1 & 2:** The total number of eligible subjects and percentage of those recruited and enrolled within 6 months of start date as tracked in a study specific screening log.

**Aim 7:** To determine the drop-out rate of subjects in Stage 1 and Stage 2.

**7a. Stage 1 & 2:** The percentage of enrolled subjects who drop-out of either study stage before the final study visit due to withdrawal by subject or lost to follow-up, and not due to death, withdrawal by study staff or PI discretion.

### 1.1.3 Exploratory Aims

The exploratory aims of this trial include measuring clinical changes for possible inclusion in the future trial.

- 1) To determine if MTM in Stage 2 improves the subject's nutritional intake by measuring the proportion of subjects who meet protein intake goals (1g/kg/day) and caloric intake goals (30c/kg/day) as assessed using the 24-Hour Diet Recall and/or VioScreen FFQ from baseline to 9 weeks.
- 2) To determine whether MTM in Stage 2 improves reported cognitive function.
  - Comparison of Encephalapp Stroop scores from baseline to 11±2 weeks. We aim to evaluate whether there is normalization in individual scores, by comparing the proportion of subjects with a 'normal' score at baseline to 11±2 weeks, with a score of < 190 seconds defined as normal.
  - Comparison of Animal Naming Test (ANT) scores from baseline to 11±2 weeks and 24±3 weeks. We aim to evaluate whether there is normalization in scores, by comparing the proportion of subjects with a 'normal' score at baseline to 11±2 weeks and 24±3 weeks, with a score of >10 animals defined as normal.
- 3) To determine if MTM in Stage 2 improves self-reported HRQOL.
  - Comparison of Short Form-8 Health Survey (SF-8) score from baseline to 11±2 weeks and 24±3 weeks. We aim to determine the proportion of subjects who experience ≥5% improvement in SF-8 score from baseline to 11±2 weeks and 24±3 weeks.
- 4) We will explore patient satisfaction and preferences of MTM with a qualitative assessment conducted at the final study visit conducted via phone at 24±3 weeks.
- 5) We will explore if MTM in Stage 2 improves health outcomes and healthcare utilization rates including:
  - Healthcare Utilization: We will compare number of reported total hospital days, number of Emergency Room (ER) visits, number of paracenteses, number of all-cause hospitalizations, number of hospitalizations due to overt HE and number of subjects who undergo liver transplantation or die at different time points throughout the study, ranging from 90 days prior to enrollment to 24±3 weeks.
  - Clinical Outcomes: Comparison of MELD-Na score, serum albumin concentration, diuretic dose, weight, and HE therapies at different time points throughout the study, ranging from 90 days prior to enrollment to 24±3 weeks.



## **1.2 END POINTS**

### Primary Endpoints

#### Stage 1:

1. The subject retention rate at 4±1 weeks post – baseline.

#### Stage 2:

1. The subject retention rate at 24±3 weeks post – enrollment.
2. The MTM intervention adherence rate at 9±2 weeks post – enrollment.

### Secondary Endpoints

#### Stage 1:

1. The proportion of subjects who complete all 24-hour Diet Recall interviews by Study Day 17 post – baseline.
2. The proportion of subjects who complete all assessments and procedures by 4±1 weeks post – baseline.
3. All subjects will be followed until death, liver transplantation or final study visit at 4±1 weeks post – baseline.

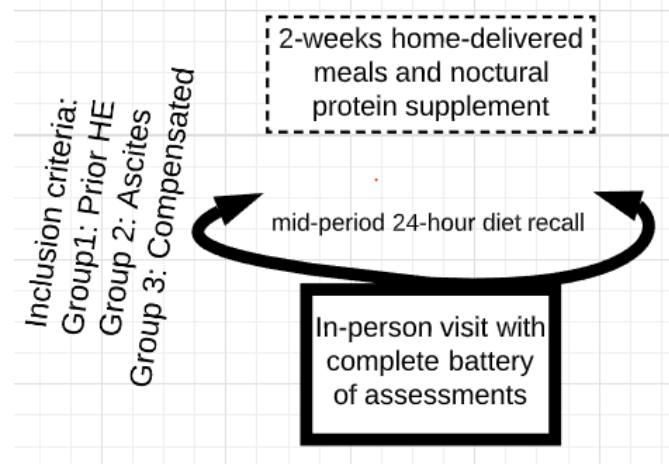
#### Stage 2:

1. The proportion of subjects who complete all 24-hour Diet Recall interviews at 9±2 weeks post – enrollment.
2. The proportion of subjects who complete all study procedures and assessments by 24±3 weeks post – enrollment.
3. Healthcare utilization rates and clinical outcomes through 24±3 weeks post – enrollment.
4. Comparison of ANT and SF-8 scores at 11±2 weeks and 24±3 weeks post – enrollment.
5. Comparison of Encephalapp Stroop score at 11±2 weeks post – enrollment.
6. All patients will be followed until death, liver transplantation or final study visit at 24±3 weeks post – enrollment.

## **2. STUDY DESIGN**

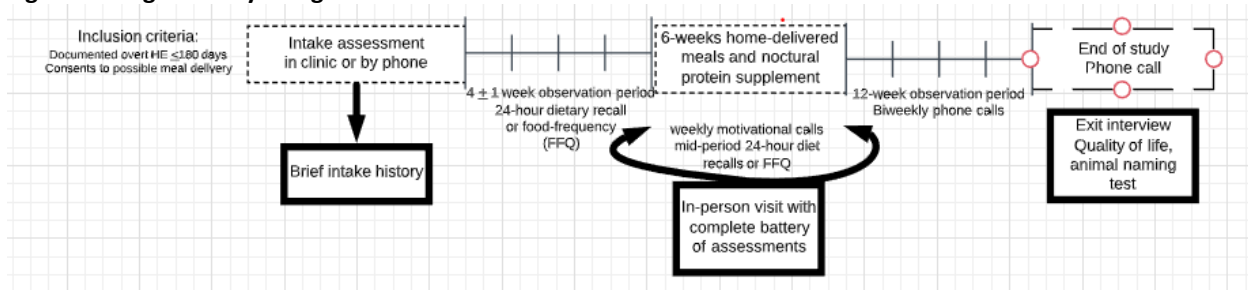
Overview: We propose a two-stage trial to determine the feasibility of MTM intervention in cirrhosis patients with a history of HE. Stage 1 will assess the feasibility of 10 different assessments and 2 weeks of MTM among three different cirrhosis populations, 1) patients with a history of ≥ Grade 2 HE, 2) patients with a history of moderate to severe ascites and 3) patients with compensated cirrhosis to determine if any of the feasibility concerns are specific to particular cirrhosis complications. Patients from each group will be enrolled in equal proportion with a total of at least 30 subjects. Baseline assessments will be conducted in person at baseline and at the final study visit after completion of 2 weeks MTM intervention at 4±1 weeks.

**Figure 1. Stage 1 Study Design**



Stage 2 is a pre-post trial after refining selection of assessments based on subject ability to complete procedures and detect changes in outcomes of Stage 1. We will enroll at least 20 subjects with a history of  $\geq$  Grade 2 HE. This stage begins with a 4 $\pm$ 1 week run-in phase with patients enrolled in person or via phone. Patients are observed in this run-in period to demonstrate interest in completing the study. Subjects will return to the clinic for a study visit in order to complete baseline assessments. Subjects in Stage 2 subjects will receive 6 weeks of MTM. During the intervention phase, subjects will receive weekly phone calls and will also be required to complete dietary recall assessments in order to measure whether they are consuming the MTM. After completion of MTM intervention, subjects will return to the clinic for an in person visit where they will repeat all baseline assessments. Thereafter, there is a 12-week observational period. Subjects will complete their final study visit and exit interview via phone between Weeks 21 and 27; Study Days 150 – 194 (SD 172 $\pm$ 22) in order to complete final assessments.

**Figure 2. Stage 2 Study Design**



## 3. SELECTION AND ENROLLMENT OF SUBJECTS

### 3.1 INCLUSION CRITERIA

**Stage 1** and **Stage 2** require different inclusion criteria and they are identified below:

**Stage 1:** We will enroll three groups of subjects with specific inclusion criteria in equal proportion (10 of each). All subjects in each group must meet the following criteria:

1. *Adult  $\geq$  18 years of age*
2. *Diagnosis of cirrhosis – must meet one of the following criteria:*
  - a. *liver biopsy, OR*
  - b. *history of cirrhosis complication: ascites, variceal bleeding, hepatic encephalopathy, OR*
  - c. *2 of the following 4 criteria:*
    1. *US, CT or MRI imaging findings of cirrhosis (cirrhotic appearing liver, splenomegaly, varices, ascites)*
    2. *Fibroscan liver stiffness score  $>13$  kPa*
    3. *Laboratory testing: AST/platelet ratio index (APRI)  $>2.0$*
    4. *CT, MRI or EGD showing presence of esophageal varices*

The additional inclusion criteria for each group is identified below:

3. **Group 1:** *Patients with history of  $\geq$  grade 2 HE within 180 days of enrollment based on review of clinical documentation verifying the event. If a description of HE symptoms is provided in clinical documentation, but it is unclear if it meets Grade 2 criteria, the PI will assess the clinical documentation and provide an HE grade.*
  - *HE is a clinical diagnosis that is defined by the following grades below. The operational definition of prior HE is an episode of gross disorientation and alterations in consciousness (lethargy to coma) that is reversible with medical therapy (lactulose and hydration):*
    1. *Grade 1: Changes in behavior with minimal change in level of consciousness*
    2. *Grade 2: Asterixis or gross disorientation, drowsiness, inappropriate behavior, euphoria*
    3. *Grade 3: Marked confusion, incoherent speech, sleeping most of the time but arousable to vocal stimuli*
    4. *Grade 4: Comatose, unresponsive to pain; decorticate or decerebrate posturing*
4. **Group 2:** *Patients with  $\geq$  moderate ascites (with or without history of HE) based on review of clinical documentation verifying ascites severity.*
  - *Ascites severity is graded as follows:*
    - i. *Mild: Trace fluid present in imaging or no fluid found on exam or in imaging while the patient is on diuretics.*
    - ii. *Moderate: Fluid detectable on imaging or exam, may be evidence by abdominal distention.*
    - iii. *Severe: Large volume of fluid present in imaging, marked abdominal distention found on exam, and/or patient required recent paracentesis.*
5. **Group 3:** *Patients with compensated cirrhosis based on review of clinical documentation verifying that the patient does not have any history or current evidence of decompensation (e.g. HE, ascites, variceal hemorrhage), but was diagnosed with cirrhosis by the criteria listed above.*

**Stage 2:** We will only enroll subjects with history of HE. All subjects in Stage 2 must meet the following criteria:

1. *Adult  $\geq$  18 years of age*
2. *Diagnosis of cirrhosis will be based upon:*
  - a. *liver biopsy, OR*
  - b. *history of cirrhosis complication: ascites, variceal bleeding, hepatic encephalopathy, OR*
  - c. *2 of the following 4 criteria:*
    1. *US, CT or MRI imaging findings of cirrhosis (cirrhotic appearing liver, splenomegaly, varices, ascites)*

2. *Fibroscan liver stiffness score >13 kPa*
3. *Laboratory testing: AST/platelet ratio index (APRI) >2.0*
4. *CT, MRI or EGD showing presence of esophageal varices*
3. *Patients with history of  $\geq$  grade 2 HE within 180 days of enrollment based on review of clinical documentation verifying the event. If a description of HE symptoms is provided in clinical documentation, but it is unclear if it meets Grade 2 criteria, the PI will assess the clinical documentation and provide an HE grade.*
  - *HE is a clinical diagnosis that is defined by the following grades below. The operational definition of prior HE is an episode of gross disorientation and alterations in consciousness (lethargy to coma) that is reversible with medical therapy (lactulose and hydration):*
    1. *Grade 1: Changes in behavior with minimal change in level of consciousness*
    2. *Grade 2: Asterixis or gross disorientation, drowsiness, inappropriate behavior, euphoria*
    3. *Grade 3: Marked confusion, incoherent speech, sleeping most of the time but arousable to vocal stimuli*
    4. *Grade 4: Comatose, unresponsive to pain; decorticate or decerebrate posturing*

### **3.2 EXCLUSION CRITERIA**

The following exclusion criteria applies to all subjects in both stages.

1. *Non-English speaking*
2. *MELD Score > 20*
3. *Pregnancy (self-reported)*
4. *Unable or unwilling to provide consent*
5. *History of liver transplant*
6. *Current or planned admission to a nursing facility*
7. *Serum creatinine  $\geq$  2.0 mg/dL (with the exception that we will include patients with a serum creatinine  $\geq$  2.0 mg/dL if they are receiving hemodialysis)*
8. *Disorientation at the time of enrollment*
9. *Barcelona-Clinic Liver Cancer (BCLC) Stage D Hepatocellular Carcinoma with Child-Turcotte Pugh (CTP) Class C*
10. *History of eating disorder*

### **3.3 STUDY ENROLLMENT PROCEDURES**

#### **3.3.1 Identification and recruitment**

After IRB approval, we will obtain informed written consent for participation from at least 50 subjects (up to 80 subjects) at the University of Michigan Health System (UMHS). However, if we are required to move to remote procedures, we will obtain verbal consent via phone with a waiver of documentation. Stage 1 will enroll up to 30 subjects and Stage 2 will enroll at least 20 subjects. If subjects drop-out, withdrawal or become lost to follow up before the final study end point, the study team will enroll additional subjects to account for the loss. Patients will be identified by one of 5 methods: 1) referral by UMHS Liver Clinic providers, 2) screening of clinic schedule on the outpatient or transplant liver service, 3) referral from study coordinators of pre-existing registry studies at UMHS, 4) screening of hospitalized patients and 5) screening of patients scheduled for paracentesis or endoscopy in their respective procedure rooms. The PI will review all potential patients before the study coordinator approaches the patient to verify eligibility.

**3.3.2 Monitoring of recruitment targets**

Data will be collected on all patients who are screened. A screening log will be maintained and will include the inclusion/exclusion criteria in Sections 4.1 and 4.2 above, and hence confirm eligibility or provide the reasons for ineligibility, as well as reasons for nonparticipation of eligible subjects. This will include: 1) the number of all persons screened with HE (Stage 1 & 2), ascites (Stage 1) and compensated cirrhosis (Stage 1), 2) reasons for exclusion (specific criteria), 3) the number approached for participation, 4) the number enrolled, 6) the number who declined participation and 7) reasons for nonparticipation.

**3.3.3 Consent Procedures**

A study coordinator will obtain informed consent. If study procedures are being conducted in person, patients will be approached at the time of previously scheduled clinic appointments, procedures, or during hospitalizations. The study coordinator will obtain written informed consent during the in-person interaction. A copy of the signed ICF will be provided to the subject. If procedures are being conducted remotely, patients will be approached via phone. If the patient would like to participate in the study, they will be consented via phone but will not be required to sign an ICF with IRB-approved waiver of documentation. The date, time and coordinator who conducted consent will be documented. A copy of the informed consent form will be made available to the patient via email or mail, whichever is their preference. After consent procedures are complete, the study coordinator will also collect subject contact information.

**4. STUDY INTERVENTIONS AND PROCEDURES****4.1 ASSESSMENTS**

The following assessments will be completed at various time points with subjects in Stage 1 and Stage 2:

**1. Demographics Questionnaire (DQ) (Appendix A)**

Records will be reviewed and/or the participants will be asked to provide the following demographic information:

1. Sex
2. Age
3. Date of birth
4. Ethnicity
5. Race
6. Highest education level attained
7. Marital status
8. Occupation status
9. Income
10. Geographic description of residence

**2. Short Form-8 Health Survey (SF-8) (Appendix B)**

The SF-8 is an abbreviated version of an original 36-item health survey (SF-36). It is a generic multipurpose quality of life instrument. It contains psychometrically based physical and mental health summary measures. The eight domains include general health, physical functioning, role physical, bodily pain, vitality, social functioning, mental health and role emotional.

**3. PROMIS Short Form 4a (General Self-Efficacy) (PROMIS SE) (Appendix C)**

The PROMIS Self-Efficacy is a 4-item questionnaire to assess the patient's self-reported current level of confidence in managing chronic conditions.

4. EncephalApp – Stroop Test

A computerized, timed test of attention conducted on an iPad or smart device via a phone application that asks patients to identify the color of words. The score is the sum of the time it takes to complete color-word concordance and color-word discordance. A score of < 190 is considered 'normal' cognitive function. Subjects who are color-blind will be excluded from performing this test.

5. Liver Frailty Index (LFI)

The LFI is composed of 3-performance based tests and is a tool specifically developed in patients with cirrhosis to objectively measure physical function. The 3 tests are:

1. 30-sec Chair Stands: A functional analogue of lower extremity strength and a commonly used test, it is the number of rises from a seated to standing position in 30 seconds.
2. Hand grip Strength: The average of three trials, measured in the subject's dominant hand using a hand dynamometer.
3. Balance Test: The number of seconds that the subject can balance in three positions (feet placed side-to-side, semitandem, and tandem) for a maximum of 10 seconds each.

6. Animal Naming Test (ANT)

The animal naming test is a timed test that consists of subjects listing as many unique animals as possible in 60 seconds. This is a validated test used for the assessment of hepatic encephalopathy.

7. VioScreen Food Frequency Questionnaire (VioScreen FFQ)

The VioScreen FFQ is a web-based dietary analysis software. It uses graphics (approximately 1200 food images), branching questions and up-to-date nutrition databases to generate detailed reports on nutrient intakes and food use patterns for the previous 90 days. It queries about 155 food and beverage items under 20 section headings: Cereals & Breads; Eggs & Meats; Chicken & Fish; Mixed Dishes & Pasta; Asian, Mexican & Soy Foods; Soups; Cheese & Dairy Products; Salads & Salad Vegetables; Garden Vegetables; Potatoes, Beans & Rice; Oil/Fat Used in Cooking; Sauces & Seasonings; Fruits; Sweets; Chips, Crackers & Snacks; Meal Replacement Drinks, Sports & Granola Bars; Milk, Coffee & Tea; Soft Drinks, Water & Juice; Alcoholic Beverages; and Supplements. Up to six graphical portion size options (i.e., different amounts of each food item displayed on a plate) are provided. The VioScreen FFQ has been scientifically validated for use in adults, and is self-administered online via computer, tablet or phone.

8. PROMIS Short Form 6a (Instrumental Support) (PROMIS IS) (Appendix D)

The PROMIS Instrumental Support is a 6-item questionnaire to assess the patient's self-reported perceived availability of assistance with material, cognitive or task performance.

9. Health History Questionnaire (HHQ) (Appendix E)

Records will be reviewed and/or the participants will be asked to provide the following information:

1. Cause of cirrhosis (confirmed with record review)
2. History of liver cancer (confirmed with record review)
3. Liver transplant status
4. Driving status
5. Disability status (Katz-ADL)
6. Current addiction or substance abuse

7. Hospitalization within past 90 days
8. Emergency Room visit within past 90 days
9. Ascites status
10. Currently taking diuretics (confirmed with record review)
11. Paracentesis within past 180 days
12. Medications taken for HE (confirmed with record review)
13. Falls in past 4 weeks

**10. 24-hour Dietary Recall**

Food recalls are a common and accurate method of assessing dietary intake in adults. All foods and beverages consumed within the past 24-hours will be recorded using the USDA 5-pass method built into the Nutrition Data System for Research (NDSR) program. Nutrition Assessment Laboratory (NAL) dietitians have been trained and standardized to complete dietary recalls. Specific forms may be utilized to assist participants in the estimation of portion size. In order to reduce error, quality control measures are both built into the NDSR program and are employed after data collection is complete by NAL management. NDSR data output provides a series of files to allow nutrient analysis per ingredient, food, meal, and day. Food group serving count information for 168 food subgroups is also provided per food, meal, and day. The 24-hour dietary recall will be conducted by NAL dietitians at the University of Michigan Nutrition Obesity Research Center via phone.

**11. Exit Interview (Appendix F)**

An 11-item questionnaire containing multiple choice and open-ended questions to assess the subjects preferences and satisfaction with MTM and the nutrition education handout.

**4.2 STAGE 1 PROCEDURES****4.2.1 Enrollment & Baseline**

For Stage 1, subjects will be primarily consented and enrolled in person at the time of a previously scheduled appointment or procedure. All subjects will provide their contact information and complete baseline assessments in person on the date of enrollment. The date subjects complete the baseline assessments is Study Day 1. If we are conducting procedures remotely, consent and baseline assessments will be completed with subjects via phone by a study coordinator. The study coordinator will track and document the amount of time it takes for subjects to complete each assessment. The total time includes the amount of time it takes to provide instruction to the subject, the amount of time it takes for the subject to answer all questions or complete all performance measures and any additional time required to answer questions the subject has. If the assessments will be completed with subjects in person, they will be conducted in the following order:

1. Demographics Questionnaire
2. SF-8
3. PROMIS SE
4. EncephalApp Stroop
5. Liver Frailty Index
6. ANT
7. VioScreen FFQ
8. PROMIS IS

**9. Health History Questionnaire**

If the assessments will be completed with subjects via phone, the EncephalApp Stroop and Liver Frailty Index will not be conducted. They will be conducted in the following order:

1. Demographics Questionnaire
2. SF-8
3. PROMIS SE
4. ANT
5. PROMIS IS
6. Health History Questionnaire
7. VioScreen FFQ

**4.2.2 Intervention**

After baseline assessments are complete, the following steps to implement the MTM intervention will occur on Study Day 1 in clinic with subjects in all three arms of Stage 1:

1. All subjects will receive Standard of Care (SOC), which is a standardized nutrition education handout containing instructions on following a high-protein<sub>±</sub>sodium restricted diet (depending on the presence of ascites). The 10 subjects within the ascites arm will receive additional information regarding the low-sodium diet.
2. All subjects will enroll in MTM designed and prepared by PurFoods, LLC (Des Moines, IA). PurFoods specializes in providing home-delivered, specialized dietician-curated meals to patients with various medical conditions such as liver disease, chronic kidney disease, cancer and cardiovascular disease. Additional information about the company and their services can be found here: <https://www.momsmeals.com/>. Subjects will receive meals that adhere to specified nutritional targets dependent upon their cirrhosis complications. If the subjects are in the compensated cirrhosis or history of HE groups, they will receive high-protein (approx. 1g/kg/day) and high-calorie high-protein and high-calorie meals that are also low-sodium ( $\leq 2000$ g/day). The study coordinator will place an order with PurFoods for each subject on Study Day 1. Study food will be pre-packaged for storage with preparation (typically microwave heating) to be completed at home by the subject.
3. In addition to home-delivered meals, the study coordinator will provide each subject with a daytime and nighttime protein supplement (approx. 15g protein) to be consumed daily at home during the same study days as MTM. The daytime protein supplement is a protein bar (ZonePerfect or Perfect Bar). The protein supplements will be provided to subjects in person after baseline completion or the study coordinator will ship them to the subject's home if in remote operations.

ZonePerfect Classic protein bars are shelf stable and contain 10 - 15g of protein per serving (1 bar). They do not contain any artificial sweeteners, flavors or colors. They come in the following flavors: strawberry yogurt, chocolate mint, oatmeal chocolate chunk, chocolate caramel cluster and others. Additional information can be found here: <https://zoneperfect.com/products>



The Perfect Bar is a refrigerated protein bar 14 – 17g of protein per serving (1 bar). Their primary source of protein are nut butters. They do not contain any artificial sweeteners, flavors or colors. Many of the flavors are lower in sodium (30-50g per serving), so these will function as a good option for subjects with ascites. They come in the following flavors: peanut butter, almond butter, blueberry cashew, mocha chip, among other. Additional information can be found here: <https://perfectsnacks.com/collections/bars>

There are two options for the nighttime supplement. The first option is a protein powder that can be dissolved in either water or milk. We are providing subjects with ProCel Chocolate Whey Protein powder which provides 15g of protein per serving. The second option is a liquid protein that can be mixed in a cup of water. We are providing subjects with LiquaCel Packets (assorted flavors) of liquid protein which provides 16g of protein per serving. Additional information regarding the protein supplements can be found here: <https://globalhp.com/shop/>

Once the MTM order is placed, subjects will receive meals at home within approximately 3 – 5 days. The MTM will be pre-packaged for storage with preparation (typically microwave heating). Subjects are instructed to start eating the meals and protein supplements the day after they receive the meals from PurFoods. Subjects will consume meals and supplements daily for 14 days, from Study Day 4(±1) to Study Day 18(±1). While the subjects are consuming MTM, subjects will undergo the 24-hour Diet Recall and VioScreen FFQ assessments between Study Days 9 – 17 (SD 13±4). A registered dietician from the University of Michigan Nutrition Obesity Research Center will call the subject directly in order to conduct the 24-hour Diet Recall via phone. The dietician will attempt to contact subjects via phone up to 4 times to complete the dietary interview. For the VioScreen FFQ, the study coordinator will send the subject a link via email so they can complete the assessment at home via personal computer, tablet or smart phone. The study coordinator will also contact the subject via phone within the same time period to conduct a motivational call. During this call the subject will ask the subject if they know their current weight, confirm that they have been eating the MTM, and ask them if they've completed the VioScreen FFQ and if they have the coordinator will ask them for their thoughts on the assessment.

### **4.2.3 Follow-Up and Outcomes**

The end point for Stage 1 is the final in-person study visit that will occur 4±1 weeks from baseline (SD 28±7). At this visit, all baseline assessments will be repeated with the subject in the same order identified above (section 4.2.1), with the exception that the Demographics Questionnaire, Health History Questionnaire and VioScreen FFQ will not be conducted. We will also conduct a semi-structured exit interview to identify the participants preferences and opinions about MTM (Appendix F). If this visit must be done remotely, the study coordinator will conduct the follow-up assessments via phone. If done via phone, like the baseline outline of remote procedures, we would not be able to conduct the EncephalApp Stroop or Liver Frailty Index. Please refer to the same order of assessments for remote procedures as specified in the 4.2.1 above. The primary outcome is the subject retention rate at 4±1 weeks post-baseline. Secondary outcomes include the proportion of subjects who complete all Stage 1 assessments and procedures 4±1 weeks post-baseline and the proportion of subjects who complete both 24-hour Diet Recall interviews by Study Day 17. Additionally, we will measure the amount of time it takes for subjects to complete all assessments and procedures and track the recruitment and drop-out rates. A review of the experience and results from Stage 1 will

inform if changes are needed to the inclusion or exclusion criteria and schedule and quantity of assessments in Stage 2.

**Table 1. Stage 1 Procedure Table**

		STUDY DAY			STUDY WEEK
	Entry/ Day 1*	4 (±1 day)	13 (±4 days)	18 (±1 days)	4 (SD 28 ± 7 days)
Informed Consent	X				
Demographics Questionnaire	X				
SF-8	X				X
PROMIS Self-Efficacy	X				X
EncephalApp	X				X
Liver Frailty Index	X				X
Animal Naming Test	X				X
VioScreen FFQ	X		X		X
PROMIS Instrumental Support	X				X
Health History Questionnaire	X				
24-hr Diet Recall			X		X
Motivational Phone Call/Exit Interview			X		X
Medically Tailored Meals		X	→	X	

\* Study Day 1 is defined as the calendar day on which the subject is enrolled/consented into the study.

## 4.3 STAGE 2 PROCEDURES

### 4.3.1 Enrollment & Baseline

For Stage 2, subjects will be primarily consented and enrolled in person at the time of a previously scheduled appointment or procedure or via phone. If we are conducting procedures remotely, consent will be completed with subjects via phone by a study coordinator. Subjects will complete the Demographics and Health History questionnaire after informed consent procedures are

completed, and will also provide their contact information. The date that subjects consent is Study Day 1.

After enrollment, there is a run-in phase until  $4\pm 1$  ( $28\pm 7$  days) weeks prior to implementation of the MTM intervention. Between Study Days 2 and 20 ( $11\pm 9$  days) of the run-in phase, subjects will undergo the 24-hour Diet Recall on two separate occasions, once either on a Tuesday or Wednesday and once on a Sunday or Monday in order to capture baseline weekday and weekend behaviors. A registered dietician from the University of Michigan Nutrition Obesity Research Center will call the subject directly in order to conduct the 24-hour Diet Recall via phone.

Baseline assessments will be conducted with all subjects at the end of the run-in phase within the  $4\pm 1$  ( $28\pm 7$  days) weeks window. The study coordinator will complete assessments 1 – 6 in person with the subject. The subject will be provided the resources (website link and login information) during their study appointment to be able to complete the VioScreen FFQ at home within 1 day of their baseline visit. If a subject does not complete the baseline appointment in person, the subject will be withdrawn by study staff at that time. The assessments will be completed with each subject in the following order:

1. SF-8
2. PROMIS SE
3. EncephalApp Stroop
4. Liver Frailty Index
5. ANT
6. PROMIS IS
7. VioScreen FFQ

If the assessments will be completed with subjects remotely via phone, the EncephalApp Stroop and Liver Frailty Index will not be conducted. They will be conducted in the following order:

1. SF-8
2. PROMIS SE
3. ANT
4. PROMIS IS
5. VioScreen FFQ

#### **4.3.2 Intervention**

After baseline assessments are complete, the following steps to implement the MTM intervention with subjects will occur in clinic:

1. All subjects will receive Standard of Care (SOC), which is a standardized nutrition education handout containing instructions on following a high-protein±sodium restricted diet (depending on the presence of ascites).
2. All subjects will enroll in MTM designed and prepared by PurFoods, LLC (Des Moines, IA). PurFoods specializes in providing home-delivered, specialized dietician-curated meals to patients with various medical conditions such as liver disease, chronic kidney disease, cancer and cardiovascular disease. Additional information about the company and their services can be found here: <https://www.momsmeals.com/>. Subjects will receive meals that adhere to their specified nutritional targets dependent upon their cirrhosis complication of hepatic encephalopathy and/or ascites. Subjects with HE will

receive high-protein (approx. 1g/kg/day) and high-calorie (approx. 30c/kg/day) meals. Subjects with HE and ascites will receive high-protein and high-calorie meals that are also low-sodium ( $\leq 2000$ g/day). The study coordinator will place an order with PurFoods for each subject after their baseline assessments are complete. Subjects will select from an available menu of meal options each week that adhere to the specified nutritional targets as above. A staff member from PurFoods will contact the subject via phone or email to complete meal selection. Study food will be pre-packaged for storage with preparation (typically microwave heating) to be completed at home by the subject and will be delivered every 1 to 2 weeks under the direction of PurFoods.

3. In addition to home-delivered meals, the study coordinator will provide each subject with a daytime and nighttime protein supplement (approx. 15g protein) to be consumed daily at home during the same study days as MTM. The daytime protein supplement is a protein bar (ZonePerfect or Perfect Bar). The protein supplements will be provided to subjects in person after baseline completion or the study coordinator will ship them to the subject's home if in remote operations.

ZonePerfect Classic protein bars are shelf stable and contain 10 - 15g of protein per serving (1 bar). They do not contain any artificial sweeteners, flavors or colors. They come in the following flavors: strawberry yogurt, chocolate mint, oatmeal chocolate chunk, chocolate caramel cluster and others. Additional information can be found here: <https://zoneperfect.com/products>

The Perfect Bar is a refrigerated protein bar 14 – 17g of protein per serving (1 bar). Their primary source of protein are nut butters. They do not contain any artificial sweeteners, flavors or colors. Many of the flavors are lower in sodium (30-50g per serving), so these will function as a good option for subjects with ascites. They come in the following flavors: peanut butter, almond butter, blueberry cashew, mocha chip, among other. Additional information can be found here:

<https://perfectsnacks.com/collections/bars>

There are two options for the nighttime supplement. The first option is a protein powder that can be dissolved in either water or milk. We are providing subjects with ProCel Chocolate Whey Protein powder which provides 15g of protein per serving. The second option is a liquid protein that can be mixed in a cup of water. We are providing subjects with LiquaCel Packets (assorted flavors) of liquid protein which provides 16g of protein per serving. Additional information regarding the protein supplements can be found here: <https://globalhp.com/shop/>

Once the MTM order is placed, subjects will receive meals at home within 3 – 5 days. The MTM will be pre-packaged for storage with preparation (typically microwave heating). Subjects are instructed to start eating the meals and protein supplements the day after they receive the meals from PurFoods. Subjects will consume meals and supplements daily for 6 weeks. Subjects will consume meals between approximately Weeks 4 – 11 of the study ( $SD\ 32\pm 8 - 74\pm 8$ ). The actual dates of MTM for each subject will be dependent upon the date they complete their baseline appointment. During the final two weeks of MTM, subjects will undergo the 24-hour Diet Recall on two separate occasions, once either on a Tuesday or Wednesday and once on a Sunday or Monday in order to capture weekday and weekend behaviors. The study coordinator will call the subject to confirm the

date the subject started eating the meals and protein supplements, the diet recalls will occur within 28 to 42 days from this date. The date the 24-hour Diet Recall is completed is dependent upon the actual dates of the final two weeks of the intervention and this will vary per subject, but it will be completed between Weeks 8 – 11 for all subjects (SD 67±14). The dietician will attempt to contact subjects via phone up to 4 times to complete the dietary interviews. The study coordinator will solicit questions related to dietary concerns during telephone calls once per week with each subject during the intervening weeks. The coordinator will also ask the subject if they know their current weight, and confirm that they have been eating the MTM.

#### **4.3.3 Follow-Up & Outcomes**

The first end point for Stage 2 is at the end of the MTM intervention. All subjects should complete the MTM intervention between Week 9 and 11; Study Days 66 and 82 (SD 74±8), barring any hospitalizations or other complications that may delay completion (see sections 4.4 and 4.5 below). The subjects will return for a second in-person visit within 2 weeks of completing intervention, between Weeks 9 and 13 (11±2 weeks); Study Days 66 and 96 (SD 81±15). At this visit, all baseline assessments will be repeated with the subject in the same order identified above (section 4.3.1). If we are conducting study procedures remotely, this visit will be conducted via phone. The EncephalApp Stroop and Liver Frailty Index will not be conducted in this circumstance. All subjects will be asked to complete the VioScreen FFQ at home within 2 weeks of completing the intervention (Weeks 9 and 13 (11±2 weeks); Study Days 66 and 96 (SD 81±15)).

Patients will then be observed for an additional 12 weeks from the date of second in-person visit. Subjects will be contacted biweekly via phone and/or email during this period to maintain contact. The main purpose of the phone calls during this time period is to maintain communication with the subject in order to prevent lost to follow-up. However, the study coordinator will also ask the subject to report their current weight. The observation period will be concluded with a phone assessment about healthcare utilization, an exit interview regarding their preferences and satisfaction with MTM (Appendix F), and the subject will also complete the ANT and SF-8. The final phone assessment represents the final end point of Stage 2 and will occur between Weeks 21 and 27 (24±3 weeks); Study Days 150 – 194 (SD 172±22).

The primary outcomes of Stage 2 are the subject retention rate at 24±3 weeks post-enrollment and the MTM intervention adherence rate at 9±2 weeks post-enrollment. Secondary outcomes measured at 24±3 weeks post-enrollment include proportion of subjects who complete all assessments and procedures, HRQOL (SF-8), cognitive function (ANT) and healthcare utilization rates and clinical outcomes. Other secondary outcomes include the proportion of subjects who complete all 24-hour Diet Recall interviews, the proportion of subjects who report improved nutritional intake and cognitive function assessed by the Encephalapp Stroop.

Table 2. Stage 2 Procedure Table

	Entry/ Day 1*	RUN-IN → BASELINE		INTERVENTION			FU 1	OBSERVATION	FU 2
		STUDY DAYS							
		11 (±9 days)	28 (± 7 days)	32 (± 8 days)	67 (± 7 days)	74 (± 8 days)	81 (± 15 days)	81 (± 15 days) → 165 (± 15 days)	172 (± 22 days)
Informed Consent	X								
Demographics Questionnaire	X								
SF-8			X				X		X
PROMIS Self-Efficacy			X				X		
EncephalApp			X				X		
Liver Frailty Index			X				X		
Animal Naming Test			X				X		X
PROMIS Instrumental Support			X				X		
Health History Questionnaire	X								
24-hr Diet Recall		2x			2x				
VioScreen FFQ			X				X		
Phone Call/Interview				6x				6x	X
Medically Tailored Meals				X	→	X			
Healthcare Utilization	CHART REVIEW →								X

\* Study Day 1 is defined as the calendar day on which the subject is enrolled/consented into the study.

#### 4.4 DISTINCT CLINICAL SCENARIO: PATIENT DEATH

In the event of a subject's death during the study period we will attempt to ascertain the date and cause of death, and healthcare utilization outcome data that is available in the subject's UMHS electronic medical record.

#### 4.5 DISTINCT CLINICAL SCENARIO: PATIENT HOSPITALIZATION

In the event of a subject's hospitalization during the study period, we will record the event as part of healthcare utilization outcome data including the number of hospital-days and the reason for

hospitalization. If the subject's hospitalization coincides with study activities, we will revise each procedure as follows:

- 1) Medically-tailored meals: If a subject is hospitalized during the MTM portion of either study stage, the study coordinator will contact PurFoods to pause future meal deliveries and ask the patient to store any meals they have at home. The subject will not be able to eat the home delivered meals during a hospitalization. Once the subject is discharged home, the study coordinator will instruct the subject to restart eating the meals they have stored at home, and will contact PurFoods to restart meal deliveries. The dates meals are stopped and restarted will be tracked.
- 2) 24-hour diet recall: If the hospitalization coincides with any of the 24-hour diet recalls, the study coordinator will contact the University of Michigan Nutrition Obesity Research Center to reschedule the assessment. The 24-hour diet recall will not be conducted while the subject is hospitalized or at a nursing facility.
- 3) In-person study visits: If the hospitalization coincides with any scheduled in-person visit, we will provide the subject an opportunity to reschedule the visit after discharge, under PI discretion.

## 4.6 EARLY TERMINATION VISIT

In the event that a subject discontinues participation in the study, they will be asked to complete all final study visit assessments and questionnaires early. If they choose not to complete them, their participation will be terminated immediately. All data collection prior to termination will be retained by the study team.

## 4.7 SUBJECT INCENTIVES

Participants in Stage 1 will be offered a \$100 compensation for completing the trial. Participants in Stage 2 will be offered a \$200 compensation for completing the trial. Participants from both stages will be offered reimbursement for mileage driven if >50 miles driven 1-way. Mileage reimbursement will adhere to the University of maximum allowable rate for federally sponsored programs and the University of Michigan which is 57.5 cents per mile. The mileage will be calculated based on distance between the Taubman Center and the subject's home address.

## 5. MANAGEMENT OF ADVERSE EVENTS AND PROTOCOL DEVIATIONS

### 5.1 PROTOCOL DEVIATIONS

Minor protocol deviations that do not impact the safety of participants or the integrity of data must be recorded and reported to the Institutional Review Board (IRB) on an annual basis as part of standard continuing review. Major protocol deviations that may impact participant safety or the integrity of data are required to be reported to the IRB as an ORIO within 7 days of knowledge of the event.

#### 5.1.2 Protocol Deviations may include the following items, among others:

- Enrollment despite meeting exclusion criteria
- Enrollment despite not meeting inclusion criteria
- Consent not obtained in accordance with IRB guidelines
- Baseline assessments collected outside of prescribed study window
- Baseline assessments not collected
- Outcome assessments collected outside of prescribed study window

- Outcome assessments not collected

## 5.2 ADVERSE AND SERIOUS ADVERSE EVENT DEFINITIONS & REPORTING

### 5.2.1 Adverse and Serious Adverse Event Definitions (AE & SAE)

In the BRAINFOOD study an AE is defined as any untoward or unfavorable physical, social or psychological occurrence in a participant that can be temporally associated with the subject's participation in the study, whether or not considered directly related to the subject's participation in the research. An AE is considered an SAE if the event results in death or permanent disability and is definitely related to the subject's participation in the study. However, due to the nature of the participants enrolled and low risk nature of the treatments, the AEs and SAEs recorded and reported to the IRB will be limited using the following guidance.

Events that are not attributable to their participation in the study will not be reported as AEs, even if the data are collected for study purposes (e.g. car accident, stroke, myocardial infarction etc.). The exception to this standard is death, which will always be reported as either an AE or SAE.

Additionally, expected clinical issues that subjects experience related to their ongoing medical care or chronic health problems will not be considered AEs unless it involves any of the above mentioned AE examples. Any AEs that are attributable to the study will be reported and adhere to the AE Reporting Timeline (see Table 3 below). The 4±1 week (Stage 1) and 24±3 week (Stage 2) end points are our final contact with subjects in which we will collect AE and SAE information. Events which qualify as AEs will be classified using the following IRB standards:

### 5.2.2 AE Relatedness and Severity

For all AEs, the PI (Dr. Elliot Tapper) will use his best judgment and indicate how related the AE is to the research procedures and intervention. He will assign the AE to one of the four categories below:

- **Definitely related:** The AE *is clearly related* to the intervention
- **Probably related:** The AE *is likely related* to the intervention
- **Possibly related:** The AE *may be related* to the intervention
- **Unlikely to be related:** The AE *is doubtfully related* to the intervention
- **Definitely not related:** The AE *is definitely not related* to the intervention

The PI will provide an AE severity:

- **Mild:** asymptomatic or mild symptoms; clinical or diagnostic observations only; no intervention indicated
- **Moderate:** minimal, local, or noninvasive intervention indicated
- **Severe:** Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling
- **Life-threatening:** Life-threatening consequences; urgent intervention indicated
- **Fatal**

The PI will AE level of expectedness:

- **Unexpected adverse events:** (i.e., has NOT been addressed or described in one or more of the following: informed consent document for this study, IRB application for this study, grant application or study agreement, protocol or procedures for this study, investigators'



brochure or equivalent (for FDA regulated drugs or devices), DSMB/DSC Reports, published literature, other documentation)

- **Expected adverse events:** (i.e., has been addressed or described in one or more of the following: informed consent document for this study, IRB application for this study, grant application or study agreement, protocol or procedures for this study, investigators' brochure or equivalent (for FDA regulated drugs or devices), DSMB/DSC Reports, published literature, other documentation, or characteristics of the study population.

### **5.2.3 IRBMED Reporting**

AEs, SAEs, UaPs and protocol deviations will be reported to IRBMED following IRBMED reporting guidelines.

## **5.3 CRITERIA OF INTERVENTION DISCONTINUATION**

If the subject experiences any SAE that might be considered related to BRAINFOOD participation, the study coordinator will inform the subject to stop all intervention activities. The PI will decide whether to continue study activities thereafter. If remaining writing prompts are discontinued, every effort will be made to maintain the subject's participation in follow-up activities.

## **6. STATISTICAL CONSIDERATIONS**

### **6.1 SAMPLE SIZE AND ACCRUAL**

The sample size for this feasibility study not driven by any hypothesis test but reflects clinical judgement. For stage 1, our prior experience suggests that 10 patients per condition is enough to detect major study barriers. For stage 2, we hope but have no way of knowing whether the intervention will impact the outcomes given its novelty. It is for that reason that we are conducting a pilot with a reasonable number of patients where outliers would not drive results.

### **6.2 DATA ANALYSIS**

#### **6.2.1 Quantitative Analysis**

We have prespecified feasibility criteria for many outcomes on the basis of proportions and timing. All outcomes will be categorized if dichotomous and compared between groups using Fisher's exact method. All timed variables will be compared using T testing. In stage 2 we will modify the testing to account for paired values from the same individual (e.g. Paired Student's T).

## **7. DATA COLLECTION AND MANAGEMENT**

### **7.1 RECORDS TO BE KEPT**

All data will be entered into case report forms (CRFs) using a REDCap platform. These forms include enrollment, baseline, intervention and outcome assessments. All data recorded in REDCap is identified by a unique Study Identification Number (Subject ID). The subject must read, understand and sign an IRB approved informed consent form (ICF). The Investigator will retain the original signed consent form in a secured location. Additionally, we will upload a copy of original signed ICF into the subject's UMHS medical record. Separate documents, including the results of the 24-hour Diet Recall will be de-identified and stored in the University Share Drive.

## **7.2 ROLE OF DATA MANAGEMENT**

The primary study coordinator will be responsible for data management. The study portal will provide a highly structured repository to store and process study data from electronic case report forms (e-CRFs), as well as to protect its integrity and confidentiality. This tool will assist study staff by providing efficient protocol management and study retention and oversight. Access to the study portal will be granted by the Investigator or primary study coordinator with differential access rights based on role.

### **7.2.1 Data Collection Protocol**

- For enrollment, study staff will access the REDCap study portal via the web, and provide screening information about the patient.
- Study-related data, as outlined in the intervention procedures above, will be entered online by research staff into the CRFs within the REDCap study portal.
- The data derived from the 24-hour dietary recalls and VioScreen will be de-identified and uploaded into REDCap.

## **7.3 DATA SECURITY AND CONFIDENTIALITY**

We will keep a separate password protected screening log and subject tracker on the University shared drive in a secured location. Only study personnel will have access to the electronic screening log that maps the Subject ID number and Screening ID number (if applicable) to the subject's name, medical record number (MRN) and contact information. Only limited identifiable data will be collected. All subject data recorded on paper are maintained in locked file cabinet with limited access by research staff.

No one other than the research team at the University of Michigan and the University of Michigan Nutrition Obesity Research Center staff members completing the 24-hour diet recall will be given or have access to your name, address, hospital registration number, and other personal identifying information. Staff members completing the 24-hour diet recall will only have access to your name, phone number, date of birth, and sex. Your name will only be used during the phone call and will be stored separately from the diet recall data. The dietitians will not have access to the study screening log or the REDCap database. They will be notified by study staff members or via an automated REDCap email reminder that the subject is due for 24-hour Diet Recall.

## **8. HUMAN SUBJECTS**

### **8.1 INSTITUTIONAL REVIEW BOARD AND INFORMED CONSENT**

This protocol, the informed consent document, and any subsequent modifications will be reviewed and approved by the Michigan Medicine IRB (IRBMED). The consent form will describe the purpose of the study, the procedures to be followed and the risks and benefits of participation. A copy of the consent form will be given to the participant, a copy uploaded to MiChart, and the original signed consent will be stored by the coordinator in a secure location. If any changes are made to the Stage 2 protocol based on the results of Stage 1, a protocol amendment will be submitted IRBMED for approval of all changes prior to start of enrollment.

### **8.2 SUBJECT CONFIDENTIALITY**

All subject evaluation forms and other records will be identified only by the Subject ID and date of completion, to maintain subject confidentiality. All records will be kept in a locked file cabinet. All computer entry will be performed using Subject ID only. Any clinical information will not be released without written permission of the subject, except as necessary for monitoring by the IRB.

## 8.3 POTENTIAL RISKS AND BENEFITS

There is minimal medical risk to any participant in this study. Patients will be counselled on the risk of cirrhosis complications (ascites, HE) that may be related to their underlying disease as well as risks associated with meals (infections, nausea). Participants can withdrawal at any time. The potential benefits to participants include an improvement in QOL and reduction in ascites and the risk of HE.

The known or expected risks are:

- **Questionnaires:** Many of the questions relate to how the subjects are feeling, and this may lead to an emotional reaction. To minimize these risks, questions will not ask explicitly sensitive information and study coordinators will be available for support. Additionally, should the questionnaires or surveys become uncomfortable, subjects can choose to skip any question that they do not wish to answer or stop at any time.
- **Loss of confidentiality:** There is rare risk of loss of confidentiality or privacy. To reduce the risk of loss of confidentiality, trained members of the research team will ask subjects questions in a private patient room. Researchers will only provide (to the professionals trained in diet recall) the minimal amount of identifying information necessary in order to complete the diet recall. This information will be limited to the subject's name, date of birth, sex, and subject ID. The subjects name will only be used during the phone call and will not be reported with the diet recall data. Information such as the subject's full name and phone number will be recorded along with their baseline data however, this information will be stored in a locked cabinet. This data will be entered into a password-protected database where all data will be coded using a study number and only staff involved in this research will have access to the data.
- **Physical Assessments:** Assessments such as the chair stand test, 10-meter (33 feet) walk, and balance test may result in tiredness, dizziness upon standing, falling, pain, or injury. Though these risks are considered to be relatively minimal.
- **Medically Tailored Meals:** There is the possibility that these foods can cause unexpected allergic reactions or symptoms such as abdominal pain, diarrhea, nausea, or vomiting. Additionally, PurFoods provides meal delivery to the subjects home address. The researchers cannot be held responsible for meals that are not delivered for any reason.

There may be additional risks that are unknown or unexpected.

## 8.4 STUDY MODIFICATION/DISCONTINUATION

The study may be modified or discontinued at any time by Michigan Medicine IRB as part of their duties to ensure that research subjects are protected. Any changes to the protocol or consent form require a written protocol amendment that must be approved by the IRB prior to implementation. These amendments, should they be required, will become part of the protocol and maintained by the Investigator as part of study documentation. If the Investigator or study coordinator implements a protocol change prior to IRB approval, the coordinator must notify the IRB via an ORIO report.

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## APPENDICES

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## Appendix A. Demographics Questionnaire

HUM00168821

Subject ID: \_\_\_\_\_ Completion Date: \_\_\_\_\_

### BRAINFOOD Demographics Questionnaire

**Instructions:** Please answer the following demographics questions. Please note that your answers will be kept completely confidential. Please record the date the form was completed on the top of this page.

1. What is your date of birth and age in years?

Date of Birth (MM/DD/YYYY): \_\_\_\_\_ Age: \_\_\_\_\_

2. What is your sex?

☐ Male

☐ Female

☐ Other (please state): \_\_\_\_\_

3. What is your ethnicity?

☐ Hispanic or Latino

☐ Not Hispanic or Latino

☐ Unknown

☐ Not Reported

4. What is your race? (select all that apply)

☐ American Indian or Alaska Native

☐ Asian

☐ Black or African-American

☐ Native Hawaiian or Other Pacific Islander

☐ White

☐ Unknown

☐ Not Reported

5. What is the highest education level that you have completed?

☐ No schooling completed

☐ Some high school, no diploma

☐ GED or equivalent

☐ Associate degree: occupational, technical, or vocational program

☐ Associate degree: academic program

☐ Bachelor's degree (e.g., BA, AB, BS, BBA)

☐ Master's degree (e.g., MA, MS, MPH, MEng, MEd, MBA)

☐ Professional school degree (e.g., MD, DDS, DVM, JD)

☐ Doctoral degree (e.g., PhD)

☐ Nursery school to 8<sup>th</sup> grade

☐ High school graduate

☐ Some college, no degree

☐ Unknown

6. What is your marital/partner status?

☐ Never Married/Single

☐ Married

☐ Domestic Partnership

☐ Separated

☐ Divorced

☐ Widowed

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Subject ID: \_\_\_\_\_ Completion Date: \_\_\_\_\_

7. What is your current employment status?

- |   |   |
|---|---|
| <input type="checkbox"/> Employed full-time | <input type="checkbox"/> Employed part-time |
| <input type="checkbox"/> Retired            | <input type="checkbox"/> On disability      |
| <input type="checkbox"/> Not employed       |   |

8. What is your annual income?

- |   |   |
|---|---|
| <input type="checkbox"/> Less than \$10,000   | <input type="checkbox"/> \$75,000 to \$99,999   |
| <input type="checkbox"/> \$10,000 to \$14,999 | <input type="checkbox"/> \$100,000 to \$149,999 |
| <input type="checkbox"/> \$15,000 to \$24,999 | <input type="checkbox"/> \$150,000 to \$199,999 |
| <input type="checkbox"/> \$25,000 to \$34,999 | <input type="checkbox"/> \$200,000 or more      |
| <input type="checkbox"/> \$35,000 to \$49,999 | <input type="checkbox"/> Unknown                |
| <input type="checkbox"/> \$50,000 to \$74,999 |   |

9. What type of geographic area do you live in?

- ☐ Rural
- ☐ Suburban
- ☐ Urban



## Appendix B. Short Form-8 Health Survey

HUM00168821

Subject ID: \_\_\_\_\_ Study Visit: \_\_\_\_\_ Completion Date: \_\_\_\_\_

### BRAINFOOD SF-8 Health Survey

**Instructions:** This survey asks for your views about your health. This information will help you keep track of how you feel and how well you are able to do your usual activities. Answer every question by selecting the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can. For each of the following questions, please mark an [x] in the one box that best describes your answer. Please note that your answers will be kept completely confidential. Please record the date the form was completed on the top of this page.

1. Overall, how would you rate your health during the past 4 weeks?
 

☐ Excellent
 ☐ Very good
 ☐ Good
 ☐ Fair
 ☐ Poor
 ☐ Very poor
2. During the past 4 weeks, how much did physical health problems limit your usual physical activities (such as walking or climbing stairs)?
 

☐ None at all
 ☐ Very little
 ☐ Somewhat
 ☐ Quite a lot
 ☐ Could not do physical activities
3. During the past 4 weeks, how much difficulty did you have doing your daily work, both at home and away from home, because of our physical health?
 

☐ None at all
 ☐ A little bit
 ☐ Some
 ☐ Quite a lot
 ☐ Could not do daily work
4. How much bodily pain have you had during the past 4 weeks?
 

☐ None
 ☐ Very mild
 ☐ Mild
 ☐ Moderate
 ☐ Severe
 ☐ Very Severe
5. During the past 4 weeks, how much energy did you have?
 

☐ Very much
 ☐ Quite a lot
 ☐ Some
 ☐ A little
 ☐ None
6. During the past 4 weeks, how much did your physical health or emotional problems limit your usual social activities with family or friends?
 

☐ None at all
 ☐ Very little
 ☐ Somewhat
 ☐ Quite a lot
 ☐ Could not do social activities
7. During the past 4 weeks, how much have you been bothered by emotional problems (such as feeling anxious, depressed or irritable)?
 

☐ None at all
 ☐ Slightly
 ☐ Moderately
 ☐ Quite a lot
 ☐ Extremely
8. During the past 4 weeks, how much did personal or emotional problems keep you from doing your usual work, school or other daily activities?
 

☐ None at all
 ☐ Very little
 ☐ Somewhat
 ☐ Quite a lot
 ☐ Could not do daily activities

## Appendix C. PROMIS Short Form 4a (General Self-Efficacy)

HUM00168821

Subject ID: \_\_\_\_\_ Study Visit: \_\_\_\_\_ Date Completed: \_\_\_\_\_

### PROMIS General Self-Efficacy – Short Form 4a

Please respond to each item by marking one box per row.

For the next set of questions, please read each sentence and rate your level of confidence in managing various situations, problems, and events.

Rate your level of confidence.

		I am not at all confident	I am a little confident	I am somewhat confident	I am quite confident	I am very confident
1.	I can manage to solve difficult problems if I try hard enough. ....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
2.	I am confident that I could deal efficiently with unexpected events. ....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
3.	If I am in trouble, I can think of a solution.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
4.	I can handle whatever comes my way.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

## Appendix D. PROMIS Short Form 6a (Instrumental Support)

HUM00168821

Subject ID: \_\_\_\_\_ Study Visit: \_\_\_\_\_ Date Completed: \_\_\_\_\_

### PROMIS Instrumental Support – Short Form 6a

Please respond to each item by marking one box per row.

		Never	Rarely	Sometimes	Usually	Always
1.	Do you have someone to help you if you are confined to bed? .....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
2.	Do you have someone to take you to the doctor if you need it? .....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
3.	Do you have someone to help with your daily chores if you are sick? .....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
4.	Do you have someone to run errands if you need it? .....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
5.	Do you have someone to prepare your meals if you are unable to do it yourself?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
6.	Do you have someone to take over all of your responsibilities at home if you need it? .....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

## Appendix E. Health History Questionnaire

HUM00168821

Subject ID: \_\_\_\_\_ Completion Date: \_\_\_\_\_

### BRAINFOOD Health History Questionnaire

**Instructions:** Please answer the following questions about your health history to the best of your knowledge. Please record the date the form was completed on the top of this page.

1. What is the underlying cause of your cirrhosis? (check all that apply)
 

<input type="checkbox"/> Alcohol	<input type="checkbox"/> Nonalcoholic fatty liver disease (NAFLD)
<input type="checkbox"/> Hepatitis C	<input type="checkbox"/> Primary biliary cirrhosis (PBC)
<input type="checkbox"/> Hepatitis B	<input type="checkbox"/> Primary sclerosing cholangitis (PSC)
<input type="checkbox"/> Autoimmune Hepatitis	<input type="checkbox"/> Other (please specify): _____
2. Do you have a past history of liver cancer?
 

☐ Yes

☐ No
3. Do you currently have liver cancer?
 

☐ Yes

☐ No
4. Are you on the liver transplant waiting list?
 

☐ Yes

☐ No

☐ Currently undergoing transplant evaluation

☐ Recently removed from the transplant waiting list

4.1 If recently removed, how long ago was removal (in months): \_\_\_\_\_

4.2 If recently removed, specify reason for removal: \_\_\_\_\_
5. Have you stopped driving within the past 6 months?
 

☐ Yes      ☐ Stopped driving more than 6 months ago

☐ No
6. Are you dependent upon assistance from anyone for any of the following (check all that apply)?
 

<input type="checkbox"/> Bathing	<input type="checkbox"/> Getting out of bed or chair
<input type="checkbox"/> Dressing	<input type="checkbox"/> Eating
<input type="checkbox"/> Using the toilet/going to the bathroom	<input type="checkbox"/> None
7. Do you suffer from addiction or substance abuse?
 

☐ Yes

☐ No

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Subject ID: \_\_\_\_\_ Completion Date: \_\_\_\_\_

8. Have you been hospitalized in the past 90 days?

☐ No

☐ Yes, please specify why: \_\_\_\_\_

7.1 If yes, number of hospitalizations: ☐ 1 ☐ 2 ☐ 3 ☐ More than 3

9. Have you had an Emergency Room (ER) visit in the past 90 days?

☐ No

☐ Yes, please specify why: \_\_\_\_\_

8.1 If yes, number of ER visits: ☐ 1 ☐ 2 ☐ 3 ☐ More than 3

10. Do you have ascites (accumulation of fluid in the abdomen)?

☐ Yes

☐ No

☐ Unknown

11. Do you currently take diuretics/water pills (e.g. Lasix/Furosemide, Aldactone/Spironolactone)?

☐ Yes

☐ No

☐ Unknown

12. Have you had a paracentesis (a procedure to remove fluid from the abdomen) within the last 90 days?

☐ Yes

☐ No

☐ Unknown

13. Do you have hepatic encephalopathy (HE)?

☐ Yes

☐ No

☐ Unknown

14. Do you take any of the following medications (check all that apply)?

☐ Lactulose

☐ Neomycin

☐ Rifaximin

☐ Unknown

☐ Flagyl/Metronidazole

☐ No

15. Have you had any falls in the past 4 weeks?

☐ Yes

☐ No

## Appendix F. Exit Interview Guide

HUM00168821

Subject ID: \_\_\_\_\_ Completion Date: \_\_\_\_\_

### BRAINFOOD Exit Interview Guide

**Instructions:** Please ask the subject the following questions and record their answers below. Please record the date the form was completed on the top of this page.

1. How satisfied were you with the meal delivery program?

Very Dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Very Satisfied
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

2. Did you like the food?

☐ Yes

☐ No

3. Would you eat this food again?

☐ Yes

☐ No

3.1 If yes, what did you like about the meals:

3.2 If no, what didn't you like about the meals:

4. Do you have any suggestion for how to improve the meals?

- ☐ More variety in meal selection
- ☐ More flavor in the food provided
- ☐ More variety in snack options
- ☐ Larger or smaller portion sizes
- ☐ Other, please note below:

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Subject ID: \_\_\_\_\_ Completion Date: \_\_\_\_\_

5. How satisfied were you with the nutrition education handout we provided?

very Dissatisfied	Dissatisfied	neither satisfied nor dissatisfied	Satisfied	very Satisfied
				

6. Do you plan to continue to use the handout?

☐ Yes

☐ No

6.1 If yes, what did you like about the handout:

6.2 If no, what didn't you like about the handout:

7. Do you have any other comments or suggestions for how we can improve the meals?