Electronic-health Application To Measure Outcomes REmotely (EAT MORE) Clinical Trial

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INVESTIGATOR'S AGREEMENT

I have read the attached protocol entitled, "Electronic-health Application To Measure Outcomes REmotely (EAT MORE) Clinical Trial," dated 3/14/2015 version 1.0 and agree to abide by all described protocol procedures. 4. I agree not to make any clinical practice changes that would conflict with the goals and implementation of the trial. I agree to comply with the World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects, the International Conference on Harmonisation Tripartite Guidelines on Good Clinical Practice, applicable U.S. Food and Drug Administration (FDA) regulations and guidelines identified in 21 CFR Parts 11, 50, 56, and 312.7, the applicable provisions of sections 402(i) and 402(j) of the U.S. Public Health Service Acts (PHS Act) [42 U.S.C. §§ 282 (i) and (j)], amended by Title VII of the FDA Amendments Act of 2007 (Public Law No. 110-85, 121 Stat.904), local Institutional Review Board (IRB) guidelines and policies, and the U.S. Health Insurance Portability and Accountability Act (HIPAA).

Principal Investigator Signature: _____ Date: _____

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PRÉCIS

Title: ***Electronic-health Application To Measure Outcomes REmotely (EAT MORE) Clinical Trial***

Study Objectives and Clinical Phase:

This is a phase II feasibility, safety, tolerability and preliminary efficacy study of an e-Health application and in-person nutritional counseling to maintain or increase weight in patients with ALS and other neurodegenerative diseases.

Objectives and Endpoints

Primary Objectives

To study the feasibility, safety, tolerability and efficacy to maintain or increase body weight of an e-Health application and in-person nutritional counseling compared to standard of care and to each other.

Secondary Objectives

To measure the number of calories required to maintain or increase body weight in patients with neurodegenerative diseases.

Tertiary Objectives: To test the effects of an e-Health application compared to in-person nutritional counseling on survival, disease progression using the ALSFRS-R, UDysRS, or UHDRS, and on quality of life using the PROMIS SF v1.1 scale.

Background and Rationale

Progressive weight loss is a common symptom of ALS and other neurodegenerative diseases including Huntington's disease (HD) and Parkinson's disease (PD) and correlates with disease progression and time to death [1-3] [4, 5]. While nutritional interventions have been found to be effective in other chronic diseases including cystic fibrosis (reviewed in [6]) and COPD (reviewed in [7]), nutritional interventions have not been tested in a systematic way in neurodegenerative diseases.

Unintentional weight loss is common in ALS and is believed to be due to a combination of reduced caloric intake from dysphagia, anorexia, dependence on caregivers, and increased caloric needs due to increased energy expenditure [8, 9]. Kasarskis et al. first recommended increasing calorie intake in patients with ALS based on a retrospective review of ALS subjects close to the time of death, showing that these subjects consumed only 84% of the recommended daily allowance of calories [2, 10]. However the type of caloric intake and exact amount has not been adequately studied (reviewed in [11]). In our recently completed study, the Trial of High Fat/High Calorie Diet vs. Optimal Nutrition in ALS, funded by the Muscular Dystrophy Association[12], we found that participants randomized to excess calories and weight gain using a calorie-dense enteral formula had a reduced risk of dying during the study than patients randomized to calorie replacement. Given these promising results, we now wish to test whether an e-Health application designed specifically to promote hypernutrition will lead to weight gain, prevent weight loss and muscle loss, and improve survival and quality of life.

Study Design:

This is a phase II feasibility, safety, tolerability and efficacy study of an e-Health application compared to in-person nutritional counseling and standard care. Approximately 150 ALS participants and approximately 75-150 PD and HD patients at MGH will be randomized 1:1:1 to one of three interventions: medical nutrition therapy using in-person counseling vs. the e-Health Application vs. standard care.

Interventions and Duration

Administration of Intervention

The goal of the two intervention arms (medial nutrition therapy using in-person counseling or using the e-Health Application) will be modest weight gain of 0.5-1 kg/month. Participants in the in-person nutritional counseling arm will receive an initial face-to-face nutrition counseling session according to a resource book outlining the general nutritional recommendations (see Appendix 1), as well as a personalized nutrition plan with daily caloric goals. They will then receive telephone monitoring of weight with additional telephone counseling as needed between return clinic visits. Home self-reported weights in both intervention arms will be verified at routine clinic visits. Patients in the in-person counseling arm will also receive in-person nutritional counseling at every clinic visit.

Participants in the e-Health arm will receive dietary guidance from the treating RD at the baseline visit including instruction in the completion of food records and weight monitoring using the e-Health App. They will be asked to enter their dietary intake and home weights every 2 weeks. The treating RD will also have access to the e-Health App data and will be able to modify the dietary recommendations of the application according to the recorded weights.

The standard care group will receive routine nutritional counseling by a treating physician or nurse about the importance of avoiding weight loss at regular clinic visits, as is the standard of care in our Neurology clinics.

A research coordinator will collect data on adverse events, disease progression, appetite and quality of life measures in all participants, including standard care participants at month 1 by telephone and at every clinic visit, approximately every 3 months. If participants are unable to make it to the clinic, the above measures will be collected by telephone interview. The total duration of the interventions will be 6 months.

Recruitment and Randomization

Adult with ALS, PD or HD who come to the MGH Neurology clinics will be asked if they wish to participate in the study. Those who agree to participate will be randomized 1:1:1 to each of the three treatment arms using a computer generated randomization list generated by the MGH Biostatistics Center.

Statistical Methods

Statistical analyses will be performed by the MGH Biostatistics Center. The primary and secondary efficacy outcomes of change in weight and caloric intake will be compared between the treatment groups using a shared-baseline linear mixed model for correlated, longitudinal assessments of weight with fixed effects of time and the treatment x time interaction and age, gender, and baseline dysphagia and their interactions with time included as covariates and random participant specific intercepts and slopes.

Safety data will be summarized by treatment group and reported to an independent Medical Monitor every 3 months during the study. Total numbers of adverse events will be compared between groups using negative binomial regression and the proportion of participants experiencing each type of event by Fisher's exact test.

In the tolerability analyses, a subject will be regarded as a treatment success if he/she complies with at least 80% of the nutritional counseling sessions, or enters at least 80% of the required electronic data.

Sample size calculation: Using the component estimates from weight data collected in the clinical trial of Ceftriaxone in ALS [13] the effective standard deviation for rate of change in weight assuming weight assessments every 2 weeks, an annual 23% mortality rate, and 20% loss to follow-up is 0.98 kg/month. Given a sample size of 150 ALS participants randomized 1:1:1 to the two interventions and standard care will provide at least 80% power to detect a true 0.75-kg/month difference between each intervention arm and the control arm over 24 wks at a two-tailed $p < 0.027$ using Dunnett's method (testing superiority of each intervention over standard care). Based on a non-inferiority bound of 0.5 kg/month, the study will have at least 80% power to declare the e-Health intervention non-inferior to in-person consultation with an RD based on a one-tailed test at $p < 0.05$ and assuming that the two interventions are in fact equivalent.

LIST OF ABBREVIATIONS

AAN	American Academy of Neurology
AE	Adverse Event/Experience
ALS	Amyotrophic Lateral Sclerosis
ALSA	ALS Association
ALSFRS-R	Amyotrophic Lateral Sclerosis Functional Rating Scores – revised
BMI	Body Mass Index
CNAQ	Council on Nutrition Appetite Questionnaire
CRF	Case report form
CFR	Code of Federal Regulations
CNS	Central nervous system
CRC	Clinical Research Center
DM	Data Management
eCRF	Electronic Case Report Form
EDC	Electronic data capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HD	Huntington's Disease
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IRB	Institutional Review Board
MDA	Muscular Dystrophy Association
MedDRA	Medical Dictionary for Regulatory Activities
MGH	Massachusetts General Hospital
MGH-SST	MGH Swallow Screening Tool
MM	Medical Monitor
MND	Motor neuron disease
MRC	Medical Research Council
NCRI	Neurology Clinical Research Institute
NIH	National Institutes of Health
NINDS	National Institute of Neurological Disorders and Stroke
NP	Nurse Practitioner
ODBC	Open Database Connectivity
OHRP	Office for Human Research Protections
PAV	Permanent assisted ventilation
PD	Parkinson's Disease
PDF	Portable Document Format
PI	Principal Investigator
PROMIS SF v1.1	Patient Reported Outcome Measurement Information System Short Form
RD	Registered Dietitian
SAE	Serious adverse event
SDF	Source Document Form
SLP	Speech Language Pathologist
UDysRS	Unified Dyskinesia Rating Scale
UHDRS	Unified Huntington's Disease Rating Scale
VC	Vital capacity
WHO	World Health Organization

Table 1. Schedule of Activities

Schedule of Activities	Screening/ Baseline	2 week Automatic Alerts	Telephone Visits (every 2-4 weeks)	In-Person Visits (3 and 6 months +/- 1 month)
All Participant Groups including Standard Care				
Written Informed Consent	X			
Abbreviated History/Weight history	X			
MGH Swallow Screening Tool	X			X
Inclusion/Exclusion review	X			
Adverse Events			X[1]	X*
Vital Signs including Height, Weight	X			X
Clinical Laboratory Assessments	X[2,4]			X[3,4]
Disease-specific rating scales (ALSFRS-R, UDysRS, UHDRS)	X*			X*
PROMIS SF v1.1	X*			X*
CNAQ	X*			X*
Dietary Intake using 24 hour recall	X			
Dietary Intake using 4 day food records	X			X
DXA Scan (optional)	X			X (month 6 only)
In-Person Nutritional Counseling				
Nutritional Counseling per Protocol	X		X	X*
Dietary Intake using 4 day food records			X (by fax)	
Weight	X		X†	X
e-Health Application Arm				
4 days of Dietary Intake using the e-Health App	X	X		
Weight (2 days)	X	X†		X

[1] Adverse events and changes in concomitant medications will be obtained by the research coordinator telephone interview in all participants 1 month after the start of the study, including the Standard Care arm. Adverse events will also be captured at every telephone contact by the Registered Dietitian in the In-Person Nutritional Counseling arm.
[2] Screening labs to include basic chemistry, liver function tests, lipid panel, thyroid stimulating hormone (TSH), uric acid, albumin, and exploratory labs including leptin, PYY and ghrelin.
[3] Routine Safety labs to include basic chemistry, liver function tests, lipid panel, albumin and hemoglobin A1c. Six month labs will also include exploratory labs (leptin, PYY and ghrelin).
[4] Labs drawn within 4 weeks of visit for clinical or research purposes may be used for the study
* May be administered or obtained by telephone within 1 week of the scheduled in-person visit if participants are unable to come to the clinic or too fatigued to complete during their clinic visit. If participants are unable to come to clinic, a self-reported home weight will be obtained and marked as self-reported.
† Participants will weigh themselves at home following specific instructions.
Abbreviations: ALSFRS-R= Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; UDysRS= Unified Dyskinesia Rating Scale; UHDRS= Unified Huntington's Disease Rating Scale; PROMIS SF v1.1= Patient Reported Outcome Measurement Information System Short Form; CNAQ= Council on Nutrition Appetite Questionnaire;

1. STUDY OBJECTIVES

1.1 Specific Aims

The overall goal of this study is to discover a simple, effective clinical intervention to increase caloric intake in patients with ALS and other neurodegenerative diseases. Our research is based upon a convergence of preclinical, epidemiological and clinical data which suggest that hypernutrition may lead to greater survival and improved outcomes in ALS. In the High Fat/High Calorie versus Optimal Nutrition in ALS clinical trial (funded by the Muscular Dystrophy Association), we hypothesized that a dietary intervention to prevent weight loss and increase body weight could have a beneficial effect on ALS survival [12]. The results of this study showed that participants who were randomized to the high calorie/weight gain arm had a reduced risk of serious adverse events and death, as well as a trend towards slower disease progression during the study. The generalizability of this study, however, was limited by its small sample size and the fact that all participants were receiving enteral nutrition.

Our long term goal is to follow up our clinical trial results with a large efficacy study to test whether increasing caloric intake will slow disease progression and lead to greater disease survival. Improving nutritional status has been shown to improve outcomes in other chronic diseases including cystic fibrosis (reviewed in [6]) and COPD (reviewed in [7]). However the efficacy of nutritional counseling has not been tested in ALS patients (reviewed in [14]) or in other neurodegenerative diseases. We now intend to test whether an electronic health application is effective as in-person nutritional counseling for patients with neurodegenerative diseases. Our study will test whether a specially modified electronic-Health (e-Health) application can provide effective nutritional counseling, monitor weights and measure key outcomes remotely.

Primary Aims: To study the feasibility, safety, tolerability and efficacy to maintain or increase body weight of an e-Health application and in-person nutritional counseling compared to standard of care and to each other.

Secondary Aims: To measure the number of calories required to maintain or increase body weight in patients with ALS and other neurodegenerative diseases at all stages of each disease.

Tertiary Aims: To test the effects of an e-Health application and in-person nutritional counseling compared to standard of care and to each other on survival, disease progression using the ALSFRS-R, UDysRS, or UHDRS, and quality of life using the PROMIS SF v1.1 scale.

2 BACKGROUND AND SIGNIFICANCE

2.1 Background and Rationale

2.1.1 *Weight loss in Neurodegenerative disease*

Body mass index (BMI) has been found to be associated with survival in several neurodegenerative diseases including ALS[1-3] Huntington's[4] and Alzheimer's disease[15] suggesting that nutrition may play a role in these diseases. Loss of body weight and BMI is a common symptom of Parkinson's disease[16-18] and we have recently found that BMI also determines survival in PD [5]. While nutritional interventions have been found to be effective in other chronic diseases including cystic fibrosis (reviewed in [6]) and COPD (reviewed in [7]), nutritional interventions have not been tested in a systematic way in neurodegenerative diseases.

2.1.2 *Weight loss in PD*

Weight loss is common in Parkinson's disease (PD) and is hypothesized to be due to a combination of several factors including hyposmia, difficulty self-feeding, dysphagia, intestinal hypomotility, depression, anorexia, nausea, and increased energy requirements due to muscular rigidity and increased involuntary movements such as dyskinesia and tremors (reviewed in[19]). Weight loss may also be related to direct effects of dopaminergic medication on appetite[20]. While the nutritional requirements for Parkinson's disease have not been defined, there is one case report commenting on the use high-carbohydrate low-protein oral supplements to stabilize weight loss in a patient with Parkinson's disease dyskinesia[21].

2.1.3 *Weight loss in HD*

Rapid weight loss is seen in all stages of HD, even before the onset of chorea, and correlates with CAG repeat length [22]. In addition to the hyperkinetic movements which lead to increased energy expenditure, there is some data to suggest that HD patients have hypothalamic dysfunction as well leading to reduced appetite and intake [23]. Baseline BMI is also predictive of disease progression in HD [4]. Nutritional counseling is recommended for patients who have lost 10% of their body weight in the prior 3-6 months, and for patients with a BMI <20 who have lost 5% of their body weight over the last 3-6 months [24]. However the effect of nutritional interventions on HD disease progression has not previously been studied.

2.1.4 *Weight loss in ALS*

Rapid weight loss is a hallmark of ALS, due to a combination of inadequate caloric intake and a hypermetabolic state. ALS patients have also reported reduced appetite [25]. Patients are often instructed to increase their calorie intake; however studies have shown that patients not using enteral nutrition consume on average only 84% of their recommended calorie needs. Weight loss correlates with disease progression and time to death [2, 10]. Subjects with abnormally low BMI (i.e. malnourished patients) have shorter survival [2, 8-10] and we have published that there is a U-shaped survival curve in ALS with the maximum survival at BMI 30-35 (mild obesity by WHO standards)[1]. It has been hypothesized that the effect of malnourishment on survival is

confounded by disease progression, i.e. that reduced BMI is due to dysphagia, reduced calorie intake and loss of muscle mass as the disease progresses. We have shown that this effect is independent of disease severity, as BMI was still a significant predictor of survival even after adjusting for ALSFRS-R, bulbar onset, FVC, and time since diagnosis [1]. Interestingly, two recent prospective studies have also found a reduction in amyotrophic lateral sclerosis risk in patients who are overweight and obese [26, 27].

2.1.5 Hypercaloric Diets as a Potential ALS therapy

Kasarskis et al. first recommended increasing calorie intake in patients with ALS based on a retrospective review of ALS subjects close to the time of death, showing that these subjects consumed only 84% of the recommended daily allowance of calories [2, 10]. However the type of caloric intake and exact amount has not been adequately studied (reviewed in [11]). Nau et al recommended that caloric intake should slightly exceed patients' needs [28]. A recent study found that oral supplements containing a modest 35% calories from fat were slightly more effective at causing weight gain than supplements containing 0% calories from fat, however there was no placebo arm to test the effects of supplementation on survival or disease progression [29].

2.1.6 Preclinical Supporting Data

Hypercaloric diets using calorically-dense diets high in fat calories were shown to lead to increased weight and improved survival in the mutant SOD1 mouse model. Specifically, a high fat diet consisting of 38% carbohydrates, 47% fats and 15% protein (by calorie content) increased the median survival time of G93A SOD1 mice from 140 to 270 days ([30], Figure 1). A high fat diet consisting of 21% butter fat and 0.15% cholesterol (by weight) increased the mean survival of G86R SOD1 mice by 20 days in a second study [31]. A ketogenic diet consisting of 60% fat, 20% carbohydrate and 20% protein did not result in a significant increase in lifespan, however this study only enrolled 11 mice total [32]. Conversely, calorie restriction in the mutant SOD1 mouse model significantly reduces survival [33, 34].

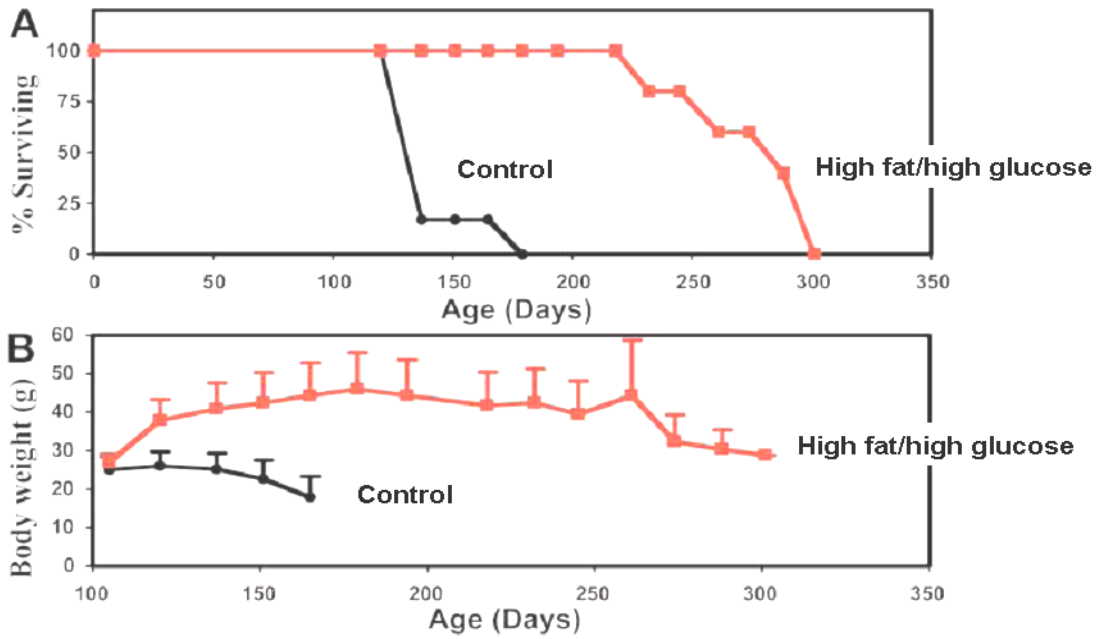

Figure 1(a): From Mattson, 2007: survival of G93A SOD1 mice on a high fat/high glucose diet consisting of 47% fat compared to a normal control mouse diet consisting of 17% fat. 12 mice were litter-matched and gender-matched and started on the diet at 6 weeks. Survival was defined as time to grade 4 paralysis. Median survival in the high fat/high glucose diet was 270 days compared to 140 days in the control group. **(b):** Average weight and S.D. for the mice in each diet group.

Based upon the preclinical mouse data and upon the epidemiologic data above, we recently completed a small phase II double-blind placebo-controlled clinical trial of a hypercaloric diets using enteral nutrition: The High Fat/High Calorie Diet versus Optimal Nutrition in ALS clinical trial, funded by the Muscular Dystrophy Association (NCT00983983)[12].

2.1.7 Human Supporting Data

In brief, in the High Fat/High Calorie Diet versus Optimal Nutrition in ALS clinical trial[12], 24 ALS receiving percutaneous enteral nutrition were randomized 1:1:1 to 100% of caloric needs using Jevity 1.0 (control diet), approximately 125% of caloric needs using Jevity 1.5 (high carbohydrate/high calorie diet, HC/HC), or 125% of caloric needs using Oxepa which contains 55% fat calories (high fat/high calorie diet, HF/HC) (all Abbott Laboratories, Abbott Park, IL) and followed for four months. Total Daily Energy Expenditure was estimated based upon Measured Resting Energy Expenditure (MREE) multiplied by their physical activity level, or participants' pre-randomization nutrition requirements, whichever was greater. Participants and evaluating investigators were blinded to treatment assignment. Primary endpoints included adverse events (AE) and compliance rates.

Seven participants were randomized to the control diet, 9 to the high carbohydrate/high calorie diet, and 8 to the high fat/high calorie arms, although four participants (1, 1, and 2, respectively) withdrew after randomization but before starting study diet. There was no imbalance in treatment allocation accross sites, and baseline demographics were similar among the three study arms. Control participants were more likely to discontinue the study diet due to adverse events

(three Cntl vs. zero HC/HC vs. one HF/HC) and less likely to complete the study on the intervention diet (17% vs. 88%, vs. 83%; p=0.03 and 0.08 for the difference in tolerability between Cntls and the HC/HC and HF/HC groups, respectively).

Participants on the HC/HC diet experienced fewer adverse events (AEs) and serious adverse events (SAEs) compared to control and HF/HC participants (24 AEs and 0 SAEs in HC/HC vs. 42 AEs and 9 SAEs in controls, vs. 49 AEs and 3 SAEs in the HF/HC arm, Appendix 1). The most common AEs were gastrointestinal (50% of HC/HC vs. 100% of Cntl vs. 100% of HF/HC). None of the participants in the two hypercaloric arms experienced elevated serum bicarbonate (compared to three participants in the control arm), as we had postulated might occur due to respiratory weakness. In addition, there were no cardiovascular AEs or SAEs in the hypercaloric arms and the HF/HC diet was not associated with increased cholesterol or hs-CRP levels (Table 3). Finally, there was no evidence that the hypercaloric diets led to diabetes based on fasting blood glucose levels and serum insulin levels (Table 3).

Participants randomized to the control arm were essentially weight-stable gaining on average 0.11 kg/month (95% CI -0.64, 0.86), although there was substantial variation in weight in the control arm (see Supplementary Figure 2A). On average, control participants consumed 1.21±0.26 times their estimated energy requirements, including both prescribed enteral nutrition and oral intake. Participants in the HC/HC arm gained on average 0.39 kg/month (95% CI -0.16, 0.95), consuming 1.54±0.33 times their estimated energy requirements. Participants in the HF/HC arm lost 0.46 kg/month (95% CI -1.11, 0.18) despite consuming on average 1.51±0.33 times their estimated energy requirements. Based on the eleven participants who underwent repeated DXA measurements after four months, participants who gained weight overall during the study gained primarily fat mass compared to LBM (2.23 ±2.25 kg vs. 0.17 ±1.29 kg) while those with net weight loss lost 1.61 ±0.99 kg LBM while still gaining a small amount of fat mass (0.39 ±0.35 kg).

Survival is shown in Figure 2. Overall, the high-carbohydrate hypercaloric arm experienced no deaths during the study while there were 3 deaths in the control arm (logrank p=0.03). The difference between the high-fat/hypercaloric and control arm was not statistically significant. In addition, the ALSFRS-R appeared to decline more slowly in the high calorie arm -1.06 (95% CI -1.71, -0.41) points/month vs. -2.17 (95% CI -3.25, -1.1) in the controls (p=0.07, see Table 1). There was no difference in the rate of decline in FVC.

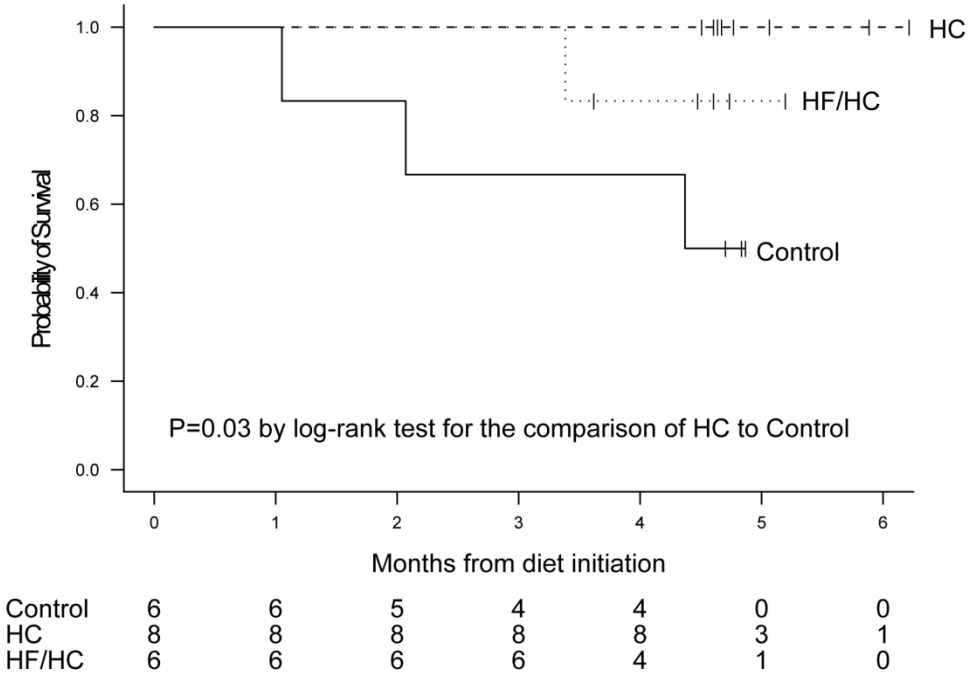

Figure 2: Kaplan-Meier curves for survival as defined by time to death or tracheotomy. The log-rank test for the difference in survival between the control and high calorie arms was significant (p=0.03).

In summary, despite the small size of this study, we believe that these results are promising and are consistent with the preclinical and epidemiologic observational data suggesting that hypercaloric diets may improve ALS survival. In addition to the survival data, the ALSFRS-R rate of decline, safety, and tolerability data all consistently favored the high calorie arm. We therefore have designed the current study to test the effects of hypercaloric diets at earlier stages of ALS, and to explore the effects of hypernutrition in other neurodegenerative diseases with unintentional weight loss.

2.1.8 Significance

Unintentional weight loss is a common symptom of all neurodegenerative diseases, and our data in ALS suggests that modifying this clinical feature may modify the progression of the underlying disease. Given that there are no effective treatments for ALS, we believe that this non-pharmacologic, supportive care intervention may offer a low-risk, cost effective approach to improving patient survival as well as quality of life.

There are currently no clinical guidelines on the type and amount of nutritional support needed in neurodegenerative diseases such as ALS, PD and HD. The observational data which we will obtain from measuring actual caloric intake and body weights during this study will allow us to estimate the nutritional requirements of participants with these diseases. Finally, this study will create a database linking micro and macronutrient intake with disease survival, which may create new hypotheses for testing nutritional interventions in the future.

2.2 Risks and Benefits of the Current Study

2.2.2 Risks of Medical Nutrition Therapy

Weight gain is an anticipated risk and would not be considered an adverse event during the trial. In the High Fat/High Calorie vs. Optimal Nutrition in ALS, we had postulated that excess calorie intake might result in increased carbon dioxide production and hypercarbia. However, using serum bicarbonate levels as a measure of hypercarbia, 3 participants in the control arm experienced hypercarbia vs. 0 participants in the two hypercaloric arms. We had also hypothesized that hypercaloric diets could lead to increased risk of vascular events (myocardial infarction, stroke or peripheral vascular disease). However, in the High Fat/High Calorie study, only one participant experienced an elevated troponin level, and this occurred in the control arm (Table 3). Diabetes was a theoretical risk from weight gain, however elevated blood glucose was not seen as an adverse event in routine safety labs. In addition, there was no increase in circulating serum insulin levels in the two hypercaloric arms.

2.2.3 Risks of Dual-energy Xray Absorptiometry (DXA)

Radiation

Those participants who consent to the optional DXA portion of the study be exposed to two DXA scans, one at the baseline and one at the final visit. The radiation exposure associated with two whole body DXA scans is approximately 0.017 milliSieverts (mSv). This amount of radiation is approximately equal to 2 day' exposure from natural background sources of radiation (cosmic rays and naturally occurring radioactive materials from the earth and the sky) [35]. This does not pose excessive risk to subjects. Female participants of child-bearing age will be instructed to use highly effective birth control for the duration of the study and will be tested for pregnancy using a urine pregnancy test immediately prior to the DXA scan.

2.2.4 Potential Benefits

Participants in this trial will benefit from frequent nutritional counseling, monitoring of weight to prevent weight loss, and possibly may gain a psychological benefit from having increased supportive care. Participants randomized to the e-Health arm will also receive an iPad for the duration of the study, if they do not already have an iPad or iPhone. In addition, there is a future benefit of furthering research and improving the care of other patients with neurodegenerative diseases. This study will test whether all multidisciplinary Neurology clinics should include a registered dietitian on their multidisciplinary staff. We will also minimize risks by collaborating with their existing clinical providers and minimizing travel for participants.

3. STUDY DESIGN

3.1 Study Design Overview

This is a phase II feasibility, safety, tolerability and preliminary efficacy study of an e-Health application versus in-person nutritional counseling to maintain or increase weight in patients with neurodegenerative disease. Approximately 150 ALS participants and approximately 75-150 PD and HD participants at MGH will be randomized 1:1:1 to one of three interventions: medical nutrition therapy using in-person counseling vs. an e-Health application vs. standard care. The total duration of the interventions will be 6 months, and participants will be asked to consent for long-term follow-up by telephone at the time of the final subject final visit. We anticipate that enrollment of the ALS participants will be completed within 12 months and the overall study will be completed within 30 months. The timing of enrollment of HD and PD participants will depend on funding and infrastructure.

3.2 Setting

The study will be conducted in the outpatient Neurology Clinics of Massachusetts General Hospital, Boston, Massachusetts. A Registered Dietitian from the MGH Clinical Research Bionutrition Center will be the head research RD for this study.

4. Study Population Selection

4.1 Study Population

Approximately 150 ALS participants and approximately 75-150 PD and HD patients will be eligible to participate. Due to the low risk of the intervention, participants will be allowed to enroll concurrently in other research studies. There will be no prohibited medications during the study, including experimental medications. The clinical trial will be advertised in the clinic using IRB approved pamphlets and posters.

4.2 *Subject Inclusion Criteria*

1. Adults with neurodegenerative diseases such as ALS, PD or HD with or without a history of unintentional weight loss.
2. Male or female subjects aged 18 years or older.
3. Participants must be capable of providing informed consent and complying with trial procedures.
4. Participants must have an MGH swallowing screening tool score≥5 at the time of the screening visit [36]
5. Participants or a designated caregiver must be able to obtain weights and communicate to their RD

4.3 Exclusion criteria:

1. Clinical evidence of unstable medical or psychiatric illness, in the investigator's judgment, which would prevent the participant from completing their assessments.
2. BMI > 35 combined with a history of cardiovascular disease; or a history of diabetes regardless of BMI.

4.4 Enrollment Procedures

4.4.1 Informed Consent

The investigator or IRB approved designee will explain the protocol and obtain informed consent from all subjects prior to initiation of any research evaluations. The investigator will determine study eligibility as determined by the inclusion and exclusion criteria. If the study subject agrees, provides informed consent, and signs the IRB approved informed consent form, the study visits are scheduled. If the subject is unable to sign the consent, they may provide verbal or typed consent and have a witness sign the consent. One copy of the signed informed consent form will be given to the subject, and another copy may be maintained in the subject's medical record. The informed consent details the potential benefits of participating in the research as well as the potential risks of the experimental interventions.

4.4.2 Randomization Process

Randomization of sites will be performed independently by the MGH Biostatistical center using a computer-generated system. Randomization will be stratified by disease group and by the presence or absence of weight loss at baseline (i.e., a decline of 5% of body weight from the time of first symptoms by self-report). Each participant will receive a unique ID number (see section 10.4.1) for data entry. This unique ID will also be used to identify the subject's Source Documents, electronic case report forms (eCRFs), and all communications. The unique ID will also be used to link the study data to the e-Health App data by having participants enter their unique ID into the e-Health App system when creating their username. Due to the design of the study, participants and evaluators cannot be blinded to treatment assignments.

5. STUDY INTERVENTIONS

5.1.1 In-Person Nutritional Counseling

The head research Registered Dietitian (RD) will provide the clinic RDs with training and guidance to ensure uniformity in nutritional counseling. Clinic RDs will be provided with a resource book, patient-oriented educational materials, and access to the head research RD for counseling support. The clinic RDs will then provide each patient randomized to the in-person nutritional counseling arm an initial face-to-face nutritional counseling session with written instructions outlining their dietary goals. This will be followed by telephone monitoring of weight with additional telephone counseling as needed between return clinic visits. Participants will complete 4-day food records at regular intervals and will fax them to the clinic RD. At every clinic visit, patients will receive in-person nutritional counseling and dietary recommendations.

For participants with ALS, we will estimate baseline caloric needs using the ALS Calorie Calculator created by Kasarskis et al.[37] . The treating RDs will counsel patients to gain weight at approximately 0.5-1 kg/month (an additional 117.5-235 kcal/day) depending on their baseline BMI and weight history (See Table 2). Based upon participants' weight gain or loss during the study, the clinic RD will be able to modify their dietary recommendations empirically. These prescribed changes will be captured as will the actual intake using 4-day food records. By

monitoring weights over time relative to actual intake, the clinic RD will be able to further refine their nutritional recommendations for each study participant.

For participants with HD, nutritional support will follow the European Huntington's Disease Network Standards of Care Dietitians Group Dietitians Group recommendations [24]with the following additional specifications: Baseline caloric needs will be calculated using the formula for total energy expenditure from Gaba et al[38], which adjusts the Harris-Benedict (HB) equation by an activity factor: [1.748 + (0.0071 × BMI)] – (0.0004 × BMI2). Additional calories will be added based upon Table 2, and the clinic RD will be able to adjust the recommended diet further based upon observed weight gain or weight loss. All prescribed dietary recommendations and participant intake will be captured electronically.

The nutritional requirements for Parkinson's disease have not been defined, although one case report commented on the use of 1000 calorie high-carbohydrate low-protein oral supplements/day to stabilize weight loss in a patient with Parkinson's disease dyskinesia[21]. We will therefore start with the HB equation, adjusted for a self-reported activity factor [39] and empirically measure the number of calories required to maintain or increase weight during the study with the weight goals in Table 2.

Table 2: Weight goals by baseline nutritional status.

Baseline BMI	Self-reported weight change since diagnosis	Weight goal during study	Calorie Goals/day
<25	Positive or negative	+1 kg/month	Deficit +235 Kcal
25≤30	<5% of body weight lost	+0.5 kg/month	Deficit +117.5 Kcal
25≤30	>5% of body weight lost	+1 kg/month	Deficit +235 Kcal
30-35	<5% of body weight lost	Weight Stability	Deficit +0 Kcal
30-35	>5% of body weight lost	+0.5 kg/month	Deficit +117.5 Kcal
>35	Positive or Negative	Weight Stability	Deficit + 0 Kcal

5.1.2 E-Health Nutritional Counseling

Participants in the e-Health arm will receive the same nutritional goals as above from the research RD using the e-Health application interface. Each participant will be asked to enter 4 days of dietary intake and 2 home weights every 2 weeks. The application will prompt them to enter their data automatically, and the research RD will receive notification of any missing data. The research RD will have access to the e-Health App data and will be able to modify the dietary recommendations made by the application according to the recorded weights using the same guideline as in Table 2.

5.1.3 Standard Care

The standard care group will receive routine nutritional counseling by a treating physician or nurse about the importance of avoiding weight loss at regular clinic visits, as is the standard of care in our Neurology clinics. All participants will be asked to complete and bring with them 4-day food records to each clinic visit.

5.2 Compliance with Dietary Recommendations (Adherence Assessment)

The treating RDs will monitor weight and dietary intake either using paper food diaries every 2-4 weeks (in-person arm) or using the self-reported dietary intake using the e-Health app to verify dietary compliance. Compliance will be defined as greater than 80% data entry using either the paper or electronic food diaries and consuming > 90% of the recommended diet.

5.3 Monitoring of Weight

Weight will be assessed at every clinic visit in all three groups. Participants in both intervention arms will be asked to weigh themselves at home or in a clinic or allied health professional office every 2-4 weeks and either enter their weights into the e-Health app or in to their Self-Weighing Log. Participants in the in-person arm will be instructed to report significant weight changes by phone to their clinic RD. The clinic RD may modify the dietary recommendations at any time based on observed weight loss, adverse events, or at their discretion. Persistent weight loss despite >90% dietary compliance will prompt an increase in target calories by 235 Kcal/day, or more if the weight loss is more than 0.5 kg/week. Changes in the dietary recommendations will be recorded in the EDC.

Any weight loss >1.5 kg during the study will prompt an increase in the frequency of telephone contact and an appropriate increase in the recommended caloric goals. In addition, any report of weight loss will prompt the treating dietitian to explore (by telephone) whether this is due to unwillingness to continue participation in the trial, inability to comply with the prescribed diet (due to weakness, dysphagia, or dependence on caregivers), or inadequate caloric recommendations. Reported dysphagia (using the swallow screening questionnaire, Appendix 9) will prompt the treating RD to refer the patient for an early in-person evaluation by their medical providers. Participants who lose more than 3 kg despite non-invasive attempts to maintain body weight will be referred to a Speech Language Pathologist for evaluation of dysphagia and possible consideration of a feeding tube.

All participants who require a feeding tube during the study will be prescribed enteral nutrition based upon results of the High Fat/High Calorie diet study. Jevity 1.5 will be prescribed at 1.5 times their calculated TDEE using the HB equation, adjusted for a self-reported activity factor [39]. Given the safety and tolerability results of this study, we do not feel that it is ethical to use a control or eucaloric diet in the standard care arm.

5.4 Concomitant Medications

Throughout the study, investigators may prescribe any other concomitant medications or treatments deemed necessary to provide adequate supportive care. All concomitant medications received by a subject will be recorded on the appropriate source documents and in the Electronic Data Capture (EDC) System.

5.4.1 Exclusionary Medications

None. Due to the low risk of the study, investigational medications will also be allowed during the trial.

6. Study Activities

6.1 Study Visits

6.1.1 Screening/Baseline Visit and Informed Consent

A schedule of activities for each intervention is provided in **Table 1.** At the screening visit, subjects will provide informed consent. Informed consent may be obtained by physicians, research nurses or study coordinators with IRB approval to consent participants in the study. No procedures will be done prior to consent. Participants will be asked basic demographic questions and will be asked for contact information for their caregivers. Participants will provide basic information about their diagnosis and disease history, such as date of diagnosis and site of symptom onset. Participants will be screened for dysphagia using the MGH Swallow Screening Tool (MGH SST) and must score at least a 5 in order to enroll (in order to ensure that they will be able to comply for 6 months with an oral diet). Participants who score below a 5 on the MGH-SST will be referred to a SLP and their treating physician and nurse will be informed. Participants who pass the MGH-SST will then be weighed and asked questions about the degree of weight loss they may have experienced since before their illness (weight loss may predate their diagnosis). Once all incusion criteria have been met, all participants will be randomized into one of the three study arms.

Additional study activities may be completed within 2 weeks of the screening/baseline visit if participants are unable to complete the activities at that time. All participants will complete a 24 hour recall. Participants in the two intervention arms will then receive written instructions with their calculated caloric goals and general dietary recommendations. Participants in the e-Health App arm who do not have access to an iPhone or iPad will be provided an iPad for the duration of the study free of cost. They will then be trained and will enter their randomization codes into the application in order to access their caloric goals and recommendations. The research RD will maintain a list linking the identification codes of the participants to their contact information. Participants will also have their blood drawn for the research and safety laboratory studies incuding a urine pregnancy test for participants who have consented for the optional DXA study. Participants who have had safety labs drawn for routine clinical (or research purposes) within 4 weeks may have their laboratory data used for the study rather than repeating the labs. Finally, participants will be given a Self Weighing Log (Appendix 1) and told to weigh themselves at least every 2-4 weeks using the log and to contact the site if they lose 3 or more pounds.

Participants who consent to the optional DXA study will be invited to go to the MGH CRC at their convenience for the DXA exam. All women of child-bearing potential will undergo a urine pregnancy test immediately prior to the DXA exam. The timing of this exam can occur within 14 days of the baseline visit.

6.1.2 Telephone Visits (Every 2-4 weeks)

The Research Coordinator on the study will contact all participants by telephone at month 1 in all arms to determine if there have been any adverse events. The Coordinator will also contact participants by telephone who are unable to return to the clinic for their routine clinic visits, in order to perform disease-related outcome measures and the quality of life questionnaire.

After the initial screening/baseline visit, the treating Registered Dietitian will monitor dietary intake and weight in the in-person arms every 2-4 weeks as necessary based upon observed weight changes. They will monitor dietary compliance by having participants complete paper food records and faxing them along with the Self-Weighing Log for review. They will then contact participants by telephone to query any weight loss or emergence of adverse events. If the treating RD identifies weight loss despite >90% compliance with dietary recommendations, they will adjust their dietary recommendations to meet the target weight from Table 2. They will then contact the study participant at least once every 2 weeks until the participant's weight has stabilized or increased. The frequency and duration of counseling sessions will be documented in the EDC.

The RD in the e-Health Application arm will contact participants who report weight loss through the App directly, through email, or by telephone if necessary. The RD will assess whether the weight loss is due to an inability to comply with the prescribed diet (due to weakness, dysphagia, or dependence on caregivers), versus inadequate caloric recommendations. Symptoms of dysphagia using the self-reported swallow screening questionnaire will prompt the treating RD to refer the patient to SLP for an early in-person evaluation.

6.1.3 Clinic Visits (Months 3 and 6)

In order to reduce the burden of research visits and data collection, in-person visits in the e-Health arm and the standard care arm will coincide as much as possible with patients' routine clinic visits. Participants wil be asked to complete a 4-day food record prior to each in-person clinic visit. At the visit, the Registered Dietitian will meet with participants in the in-person arm and will verify compliance with the prescribed diet. Participants will review the dietary goals and recommendations with participants and make adjustments as needed based upon observed weight loss. All participants will be rescreened for dysphagia using the MGH–SST and participants with dysphagia will be referred to a SLP before continuing in the study. If the SLP determines that a modification of their current diet is required, those modifications will be incorporated into the dietary recommendations. If the SLP determines that the participant cannot swallow safely, their study diet will be temporarily suspended until they can obtain a feeding tube. If they decline the feeding tube, participants will still be asked to complete the final visit by telephone and to consent for long term follow-up for survival. Participants' blood will also be drawn for research and safety laboratory studies.

6.1.4 Treatment Withdrawals and Loss to Follow-up

A subject has the right to refuse counseling sessions and contact from the RD at any time and for any reason. If participants express unwillingness to continue to participate in the trial, participants will be asked if they would be willing to be followed for telephone-based questionnaires, QOL and survival only, with a final telephone visit at 6 months. The treating RD or research coordinator will document the reasons for discontinuation in the EDC. Long-term follow-up for survival will continue until the end of the study and be included in the intention-to-treat analysis. For the primary safety analysis, telephone visits will be used to document adverse events, changes in medical history and medications. All attempts will be made to follow these subjects for all outcome measures by telephone if necessary. The analysis of data from subjects who stopped treatment and/or refused study visits is discussed in the data analysis section.

6.1.5 Final Evaluations and Post-Intervention Phone Calls

The final visit will coincide with the participant's routine clinic visit approximately 6 months after study initiation. Weight, appetite, QOL and disease-specific questionnaires will be measured. Participants will return the study iPad at this visit and all participant data will be deleted from the iPad. Participants' blood will be drawn for research and safety laboratory studies, including a urine pregnancy test if participants have consented for the optional DXA study.

One month after the final clinic visit, the research coordinator will contact all participants by telephone to document adverse events. The research coordinator will also contact subjects approximately every 6 months until all participants have finished the study, to document vital status and weight, dates of feeding tube placement, tracheotomy or death.

6.1.6 End of Study Phone Call

All participants will be contacted at the time of the last subject last visit in order to obtain vital status and dates of feeding tube placement, tracheotomy or death.

6.2 Definitions of Evaluations and Outcome Measures

6.2.1 Primary Outcome Measures

6.2.1.1 Safety and Tolerability

Safety will be evaluated using reporting of hospitalizations, deaths and other serious adverse events, and treatment discontinuations due to adverse events. Tolerability will be defined as the number of participants who do not decline nutritional counseling, i.e. the number of participants who complete the 6 months of counseling sessions in the in-person arm, or who enter at least 80% of the required data in the e-Health application arm. Tolerability will not be defined based on compliance with nutritional recommendations as compliance may be affected by other factors such as disease progression.

Adverse Events:
The research coordinator will collect data by telephone on adverse events after the first month, and at each clinic visit in all participants. Adverse events will be recorded using the MedDRA coding system. Safety labs including the basic metabolic panel, lipid profile, hemoglobin A1c and liver function tests will be performed at the Screening/Baseline and routine clinic visits.

6.2.1.2 Primary Outcome Measure: Weight

The primary outcome of weight will be compared between each intervention arm and the control arm using the measured weights from each clinic visit, approximately every 3 months. Participants will be weight lightly clothed without shoes or braces. Participants may use a chair scale or wheelchair scale if they are unable to stand. Body mass index will be calculated at the initial visit using a baseline height measurement.

Weight will also be used to direct therapy. Participants in the in-person counseling arm will be given a Self-Weighing Log to weigh themselves every 2-4 weeks, and to call the center if they experience 2 or more pounds of weight loss compared to their baseline weight. The e-Health arm will be prompted automatically by the application to weigh themselves twice every 2 weeks, and to enter the data into the application. If there is a greater than 2 pound change from the prior weight, the treating RD will be alerted and will be able to contact the participant by telephone or by instant messaging through the application to verify the weight change. They will then be able to make dietary adjustments and to monitor weights more frequently in any participant who experiences weight loss. Self-reported weights will be verified at routine clinic visits. Self-reported weights will also be used to compare the two intervention arms.

6.2.2 Secondary Outcome Measures:

In order to monitor dietary compliance and to collect comprehensive nutritional information, we will use 4 day food records in the in-person counseling arm. The e-Health application arm will be prompted every 2 weeks to report all dietary intake for 4 days (including 1 weekend day) along with their activity level and home weights (measured twice over 2 days). The 4 day food records will be analyzed using Nutrition Data System for Research (NDSR) software Version 2014 by the RD and coordinator, while the e-Health application data will automatically analyze the data into total caloric intake, percent protein, fat, and carbohydrate.

6.2.3 Tertiary Outcome Measures:

Tertiary outcome measures will be collected by a research coordinator at every clinic visit, approximately every 3 months, including standard care participants. Tertiary outcome measures will include change in disease-related questionnaires (ALSFRS-R, UDysRS, UHDRS), quality of life using the PROMIS SF v1.1 questionnaire, and the CNAQ appetite questionnaire. For participants who are unable to physically come to the clinic for their clinic visits, the patient-reported sections of these questionnaires will be administered by telephone. The study is not powered to detect changes in disease progression.

6.2.3.1 Survival:

Survival will be defined as time to death, tracheotomy or the initiation of permanent assisted ventilation (PAV). PAV is defined as noninvasive or invasive ventilation used for more than 22 hours in a 24-hour period for 14 consecutive days. Participants will also be asked to consent for long-term follow-up at the initial visit and their vital status will be determined every six months by telephone until the final participant completes the study, unless they expressly withdraw their consent.

6.2.3.2 Time to Percutaneous Endoscopic Gastrostomy (PEG) or Jejunostomy (PEJ) Placement:

Date of placement of PEG or PEJ feeding tubes will be captured using the EDC. Frequency and time to placement of feeding tubes will be compared between the different arms. We hypothesize that participants in the two intervention arms will be more willing to undergo

feeding tube placement and that there will be less weight loss before feeding tube placement in the two intervention arms.

6.2.3.3 Exploratory Outcome Measures:

Exploratory outcome measures include changes in weight, fat mass, and fat free mass using DXA scans, lipid levels, serum markers of nutritional status, and the appetite regulatory hormones Leptin, Ghrelin and PYY. Leptin is an important regulator of appetite, food intake, and energy expenditure (reviewed in [40]). Leptin is a peripherally circulating hormone produced by adipose tissue which crosses the blood brain barrier and binds to leptin receptors primarily in the hypothalamus where it leads to anorexia and weight loss. In addition to regulating appetite, leptin has also been reported to be neuroprotective in ischemic models and amyloid toxicity [41-43]. Patients with Alzheimer's disease have been shown to have lower circulating leptin levels than controls, and low premorbid leptin levels are associated with an increased risk of cognitive decline and Alzheimer's disease in two large prospective studies, even adjusted for waist-hip ratio and BMI [44, 45]. This is in contrast to the data showing that mid-life obesity is a risk factor for Alzheimer's disease. Leptin levels have not been measured in ALS except in one small study of 21 patients where the results were not compared to controls and not adjusted for BMI [46].

7. Adverse Experiences Related to Medical Nutrition Therapy

Weight gain
An increase in weight in either of the intervention arms is expected and would not be considered an adverse event. In the High-Fat/High Calorie versus Optimal Nutrition in ALS clinical trial, there were no complications of heart disease, diabetes, or breathing problems in the study arms who received hypercaloric diets. Increase in weight was seen in the high-carbohydrate hypercaloric arm and was associated with fewer AE and SAE. We will therefore tell participants that they are expected to gain weight and that we will not consider this an adverse event.

Gastrointestinal Side Effects
In the High-Fat/High Calorie clinical trial, the following adverse events were observed (Table 3). The most common adverse events were gastrointestinal and presumably related to the enteral formulae that participants received. Because the current study is designed primarily for participants taking food by mouth, we anticipate a lower frequency of gastrointestinal side effects. However, we anticipate the following common adverse events that may be observed with any nutritional intervention:

- Abdominal Fullness
- Belching
- Flatulence
- Constipation
- Heartburn

Management of Adverse Experiences
As above, weight gain would not be considered an adverse event. Weight loss will be managed by increasing the target calorie goal by 235 Kcal/day or more as measured empirically. Gastrointestinal side effects will be managed by adding over-the counter simethicone, fiber

(psyllium, cellulose, wheat dextrin), or by removing possible culprit foods such as dairy, wheat. Gastroesophageal reflux will be managed with over-the counter calcium carbonate, or if ineffective, prescription medications at the discretion of the treating physician.

Table 3. Adverse Events by Body Sytem	Type	Cntl		HC/HC		HF/HC		p values (events)			p values (% Pts)		
		N	Pts (%)	N	Pts (%)	N	Pts (%)	Overall	HC/HC vs. Cntl	HF/HC vs. Cntl	Overall	HC/HC vs. Cntl	HF/HC vs. Cntl
Allergy/Immunology	**AE**	0	0 (0)	1	1 (13)	0	0 (0)	0.81	0.69	>0.99	>0.99	>0.99	>0.99
(Allergic rhinitis)	**SAE**	0	0 (0)	0	0 (0)	0	0 (0)	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
Cardiac (Atrial fibrillation,	**AE**	2	1 (17)	0	0 (0)	0	0 (0)	>0.99	0.97	0.97	0.6	0.43	>0.99
elevated troponin)	**SAE**	0	0(0)	0	0 (0)	0	0 (0)	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
Constitutional Symptoms	**AE**	7	2 (33)	2	2 (25)	5	2 (33)	0.41	0.2	0.78	>0.99	>0.99	>0.99
(Fatigue, weight change)	**SAE**	0	0 (0)	0	0 (0)	0	0 (0)	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
Dermatology	**AE**	0	0 (0)	0	0 (0)	1	1 (17)	0.71	>0.99	0.51	0.6	>0.99	>0.99
(Abration)	**SAE**	0	0 (0)	0	0 (0)	0	0 (0)	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
Gastrointestinal (detached	**AE**	13	6 (100)	8	4 (50)	21	6 (100)	0.04	0.11	0.21	0.02	0.09	>0.99
feeding tube, bloating,													
dyspepsia, diarrhea)	**SAE**	0	0 (0)	0	0 (0)	0	0 (0)	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
Hematology/Coagulation	**AE**	1	1 (17)	0	0 (0)	0	0 (0)	>0.99	0.97	0.64	0.6	0.43	>0.99
(Thrombocytopenia)	**SAE**	0	0 (0)	0	0 (0)	0	0 (0)	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
Infection	**AE**	5	2 (33)	3	3 (38)	6	4 (67)	0.46	0.41	0.82	0.62	>0.99	0.57
(Urinary tract, pneumonia)	**SAE**	1	1 (17)	0	0 (0)	0	0 (0)	0.6	0.43	>0.99	0.6	0.43	>0.99
Metabolic/Laboratory	**AE**	2	1 (17)	0	0 (0)	0	0 (0)	>0.99	0.97	0.97	0.6	0.43	>0.99
(Elevated alkaline	**SAE**	0	0 (0)	0	0 (0)	0	0 (0)	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
phosphatase, hypokalemia)													
Musculoskeletal	**AE**	0	0 (0)	5	1 (13)	4	2 (33)	>0.99	0.97	0.97	0.45	>0.99	0.45
(Falls, weakness)	**SAE**	0	0 (0)	0	0 (0)	0	0 (0)	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
Neurology/Psychiatry	**AE**	1	1 (17)	1	1 (13)	1	1 (17)	0.97	0.9	0.99	>0.99	>0.99	>0.99
(Dizziness, depression)	**SAE**	0	0 (0)	0	0 (0)	1	1 (17)	0.6	>0.99	>0.99	0.6	>0.99	>0.99
Pain	**AE**	3	2 (33)	2	2 (25)	4	3 (50)	0.58	0.46	0.72	0.84	>0.99	>0.99
(Abdomin, neck, limb)	**SAE**	2	1 (17)	0	0 (0)	0	0 (0)	0.18	0.18	0.5	0.6	0.43	>0.99
Pulmonary/Upper	**AE**	8	3 (50)	1	1 (13)	6	3 (50)	0.16	0.075	0.72	0.28	0.24	>0.99
Respiratory (Dyspnea,	**SAE**	6	3 (50)	0	0 (0)	2	2 (33)	0.007	0.006	0.29	0.07	0.06	>0.99
hypoxia, aspiration, cough)													
Total	**AE**	42	6 (100)	23	8 (100)	48	6 (100)	0.06	0.06	0.73	>0.99	>0.99	>0.99
	SAE	9	4 (67)	0	0 (0)	3	3 (50)	<0.001	<0.001	0.15	0.03	0.015	>0.99

8. Intervention Suspension Related to Nutritional Counseling

While we do not anticipate serious adverse events from medical nutrition therapy, we will suspend the nutritional interventions while participants are hospitalized, or if participants withdraw consent during the study. If participants wish to continue in the study after discharge, they may resume nutritional counseling with the approval of their treating physician. If participants develop significant dysphagia during the study and are deemed unable to swallow safely by a Speech Language Pathologist, even with dietary modifications, the study nutritional goals will be suspended until participants are able to obtain a feeding tube. Participants who receive a feeding tube will then receive Jevity 1.5 at 1.5 times their estimated total daily energy expenditure, regardless of the study arm to which they have been randomized.

9. STATISTICAL CONSIDERATIONS

Statistical analyses will be performed by Dr. Eric Macklin of the MGH Biostatistics Center, who was the statistician on the High Fat/High Calorie vs. Optimal Nutrition in ALS clinical trial. Safety and tolerability will be assessed in all randomized participants, analyzed according to the treatment they actually received. Efficacy will be estimated from an intent-to-treat (ITT) sample, consisting of all randomized participants and analyzed according to their originally assigned treatment group regardless of adherence to that treatment. Secondary efficacy analyses will consider a per-protocol sample that adhered to their assigned treatment if this would differ from the mITT analysis for more than 10% of the sample. ALS, PD, and HD participants will be analyzed separated.

9.1 Safety and Tolerability

All randomized subjects will be considered evaluable for tolerability and safety. Subjects lost to follow-up will be considered treatment failures at the time they drop out of the study. The data will be reviewed by the independent Medical Monitor, using the considerations here as guidelines. Their recommendation would then be reviewed by the Principal Investigator.

Safety data will be summarized by disease group and treatment group and reported to the independent Medical Monitor every 3 months during the study. Total numbers of adverse events will be compared within each disease group and among treatment groups using negative binomial regression and the proportion of participants experiencing each type of event by Fisher's exact test. Every 3 months the Medical Monitor will review cumulative study reports to determine if there has been an excess rate of serious adverse events in any of the arms. At two interim analyses, mortality rates will be compared, and one or both intervention arms may be terminated for one or more disease groups according to pre-determined stopping rules described below.

In the tolerability analyses, a subject will be regarded as a treatment success if he/she complies with at least 80% of the nutritional counseling sessions, or enters at least 80% of the required electronic data.

9.2 Weight and Caloric Intake:

The primary and secondary efficacy outcomes of change in weight and caloric intake will be compared within each disease group and among the treatment groups using a shared-baseline linear mixed model for correlated, longitudinal assessments of weight with fixed effects of time and the treatment x time interaction and age, gender, and baseline swallowing score and their interactions with time included as covariates and random participant specific intercepts and slopes. Pairwise comparisons between treatment groups will be analyzed using linear contrasts from the full mode, with correction for multiple comparisons vs. standard of care using Dunnett's method. Significant benefit from the eHealth or RD intervention will be declared if less weight is lost and the two-tailed p-value for comparison to standard of care is less than 0.027 for each intervention separately.

9.3 Sample size calculation:

Using the component estimates from weight data collected in the clinical trial of Ceftriaxone in ALS [13] the effective standard deviation for rate of change in weight assuming weight assessments every 2 weeks, an annual 23% mortality rate, and 20% loss to follow-up is 0.98 kg/month. Given a sample size of approximately 150 ALS participants randomized 1:1:1 to the two interventions and standard care will provide at least 80% power to detect a true 0.75-kg/month difference between each intervention arm and the control arm over 24 wks at a two-tailed $p < 0.027$ using Dunnett's method (testing superiority of each intervention over standard care). Based on a non-inferiority bound of 0.5 kg/month, the study will have at least 80% power to declare the e-Health intervention non-inferior to in-person consultation with an RD based on a one-tailed test at $p < 0.05$ and assuming that the two interventions are in fact equivalent.

Accrual Targets: We intend to enroll 3-4 ALS subjects per week for the first 12 weeks, after which the rate will slow to 2-3 subjects/week, in order to accommodate return schedules and telephone visits. It should take approximately 12 months to enroll 150 participants at an average rate of 10 subjects per month. PD and HD subjects will be enrolled separately based upon funding and infrastructure availability.

Treatment Discontinuation Rate Targets: Subjects who discontinue treatment will be considered treatment failures in the tolerability analysis. However if there is an elevated discontinuation or study drop-out rate, it will reduce the power to detect a significant treatment difference for the primary outcome. The Steering Committee will analyze enrollment and discontinuation rates at pre-specified intervals and if it appears that fewer than 25 subjects per arm will complete the 6 month study, they may recommend increasing the enrollment times or stopping early for futility.

9.4 Tertiary and Exploratory Outcomes:

Although the study is not powered to look at the effects of the diet interventions on disease progression, we will examine trends in measures of disease progression. Preliminary analyses of survival and disease-specific outcome measures (ALSFRS-R, UDysRS, UHDRS) will use the ITT sample. We will ascertain the final outcome measures of all subjects at the end of the study and every subject will be included in the analysis whether or not they elected to stop treatment before the end of the study.

Change in the disease-related outcomes will be compared among the treatment groups using the same shared-baseline linear mixed model used to analyze weights. Additional baseline measures that might independently predict rate of progression will be considered for inclusion as additional covariates based on review of data prior to analysis for treatment differences.

Survival during and after the study intervention will be analyzed using a Cox proportional hazards model for treatment assignment, adjusted for age, gender, duration of disease, and baseline BMI. Hazard ratios and their 95% confidence intervals will be used to interpret the regression results.

The exploratory outcome measures of biomarkers of body composition, lipid metabolism, and appetite regulatory hormones will be explored in the ITT and per-protocol samples. Change over time in fat mass, fat-free mass, albumin, pre-albumin, lipid levels, leptin, ghrelin, PYY, will be compared among the treatment groups using a shared-baseline linear mixed model with gender, treatment and BMI included as covariates. We hypothesize that weight gain in the intervention arms will result in increased lipid levels. Pairwise comparisons between treatment groups will be analyzed using linear contrasts from the full model.

9.5 Stopping for Safety

The Principal Investigator is responsible for oversight of the data safety and will work with the Medical Monitor and study statistician to monitor the study and evaluate safety on an ongoing basis. Unblinded safety data will be presented to the Medical Monitor every 3 months during the study. Decisions to stop the trial, enrollment of one or more disease groups, or randomization of one of the intervention arms early for safety will be made by the Medical Monitor, Principal Investigator and study Statistician. There will be a rule for stopping if either nutritional counseling intervention appears to increase mortality relative to standard of care, where mortality is defined as death or initiation of permanent assisted ventilation. Survival in each counseling intervention arm will be compared to the standard of care arm using the logrank test. We will use an alpha spending rule to test for increased mortality with a cumulative 1-sided p-value of 0.1 separately for each disease group. By Dunnett's test, that equates to cumulative 1-sided p-values of 0.0574 for each intervention arm according to the following table:

Analysis	% of total follow-up completed	Z statistic	Cumulative Alpha	P-value to stop
1 (Interim)	33.3%	3.09103	0.000997	0.000997
2 (Interim)	66.7%	2.06168	0.019950	0.019619
3 (Final)	100%	1.63136	0.057404	0.051408

Thus, if at the first interim analysis, the p-value for the logrank test comparing the survival distributions of one of the interventions versus standard care is less than 0.000997, then this intervention arm would be stopped. Each intervention arm may be stopped early independently, without affecting continued enrollment and follow-up of participants in the other arms of the trial. The overall probability of stopping at least one arm of the trial early for a given disease group when there is in truth no effect on mortality is 10%. The probability of stopping at least one arm of the trial early across all three disease groups when there is no effect on mortality in

any is 27%. The first interim analysis will occur after one third of total expected follow-up is completed. This may vary depending on accrual rate and total accrual targets for each disease group.

10. DATA COLLECTION AND ADVERSE EVENT MONITORING

10.1 Records to be Kept and Project Organization

The MGH NCRI Data Management group and the Biostatistics Center at the MGH will conduct data management, biostatistics, regulatory compliance, adverse event reporting. For the purposes of the study, all clinical data will be captured using the NeuroBANK™ data repository platform.

10.2 PURPOSE OF NEUROBANK™

NeuroBANK™ is a collaboration and data repository platform maintained by the Massachusetts General Hospital (MGH) Neurological Clinical Research Institute (NCRI). The system conforms to the 21 CFR Part 11 and other guidance documents on computerized systems in clinical trials. This platform facilitates:

1. Capture of clinical and research data from neurologic patients for individual projects in a structured and secure system;
2. Aggregating and sharing uniform, deidentified and/or anonymized datasets for secondary analyses.

10.3 ROLE OF DATA MANAGEMENT

Data Management (DM) is responsible for the development, execution and supervision of plans, policies, programs, and practices that control, protect, deliver, and enhance the value of data and information assets.

All data will be managed in compliance with applicable Sponsor and regulatory requirements. Site personnel will collect, transcribe, correct, and transmit the data onto source documents, Case Report Forms (CRFs), and/or other forms used to report, track and record clinical research data. DM is responsible for developing, testing, and managing clinical data management activities.

10.3.1 Data Entry and Checks

Data capture will be entered in a timely manner into the NeuroBANK™ Electronic Data Capture (EDC) System. Data capture is the responsibility of the staff at the site under the supervision of the Principal Investigator. During the study, the Site investigator must maintain complete and accurate documentation for the study.

The NeuroBANK™ platform provides password protection. An edit checking and data clarification process will be put in place to ensure accuracy of the data. Logic and range checks as well as more sophisticated rules may be built into the eCRFs to provide immediate error checking of the data entered. The system has the capability to automatically create electronic

queries for forms that contain data that are out of range, out of window, missing or not calculated correctly. The sites will only have access to the queries concerning their subjects.

10.3.2 Data Lock Process

The platform will have the ability to lock the project-specific visits to prevent any modification of data once the project is closed. Once this option is activated, every user will have Read-Only access to the data. The database then will be transferred to the Biostatistics Center by unloading the relational MS SQL Server database to a SAS format for statistical analysis.

10.3.3 DATA HANDLING AND RECORD KEEPING

The Principal Investigator is responsible to ensure the accuracy, completeness, legibility, and timeliness of the data reported. Data reported in the eCRF derived from source documents should be consistent with the source documents and discrepancies should be explained.

10.3.4 Database Security

The MS SQL Server database is located on a secure database server. This server is located in a restricted area of the Partners Healthcare server farm and physical access to it is limited to authorized personnel only. Both database and Web servers are located on the Partners Healthcare network behind the firewall. Access to the data at the clinical site will be restricted and monitored through the system's software with its required log-on, security procedures and audit trail. The data will not be altered, browsed, queried, or reported via external software applications that do not enter through the protective system software. There will be a cumulative record that indicates, for any point in time, the names of authorized personnel, their titles, and a description of their access privileges. The record will be in the study documentation accessible at the site. Controls will be in place to prevent, detect, and mitigate effects of computer viruses on study data and software. The application utilizes SSL (Secure Sockets Layer) technology and 128-bit encryption to comply with requirements of 21 CFR Part 11 for Open Systems. Backups of the database will be performed nightly using the services provided by the MGH network. All PC’s run virus protection software full-time and are updated with the latest virus detection strings regularly; the Windows NT server does this as well and has the additional security of scanning all e-mail for viruses before a user can even access them. All accounts are password protected and passwords must be changed on a regular basis.

In addition, the EDC system will have an extra level of password security. At study initiation, the Data Manager will set default passwords for the relevant study personnel at the MGH NCRI and at the study site. When a new user logs in with the assigned username and default password for the first time, he or she will be forced to change the password to a unique one (at least six characters long), known only to the user. An ongoing paper log will be kept showing when usernames and passwords are set up, for whom, in what user capacity and when usernames are disabled. In case an employee forgets her/his password or a new user is added, they will submit a password request form via email to the Data Manager, who will issue a new default password. They must then go through the Change Password process. The passwords will expire every three months, when users will be required to go through the Change Password process. To avoid password-based software attacks, the system will lock a user for 1 minute if an incorrect

password is provided 3 times in a row. A user will also be able to change the password at will if he or she feels that it may have been compromised.

10.4 Confidentiality

The NeuroBANK™ software and patient data reside on servers located in the Partners Healthcare Systems (Partners) server farm. Physical and software access to the servers and security is provided by the Partners IT department. Members of the NeuroBANK™ management team will do everything, within reason, to keep a participant's identity protected.

10.4.1 Global Unique Identifier (GUID)

A patient Global Unique Identifier (GUID) will be used as the identifier for individuals participating in the study in NeuroBANK™. The GUID is an 11-character string that is generated using encryption technology and algorithms licensed by the NCRI from the National Institutes of Health (NIH).

The GUID is generated on a secure website that utilizes 128-bit Secure Socket Layer (SSL). Of note, this website is not linked to NeuroBANK™. The GUID is generated using an irreversible encryption algorithm – it accepts twelve identifying data elements, (e.g. last name at birth, first name at birth, gender at birth, day, month and year of birth, city and country of birth, etc.), and produces a unique random-generated character string, or GUID. No identifying information is stored in the system; it is simply used to generate the GUID. If the same information is entered again, the same GUID will be returned.

The GUID is entered into NeuroBANK™ when the patient is being created in the system. As the same patient may participate in multiple studies, NeuroBANK™ will also allow capturing a study-specific ID for the patient. For more information about NeuroBANK™ or the GUID, please go to: www.neurobank.org.

10.4.4 Quality Assurance

The Principal investigator will be responsible for ensuring that informed consent is properly obtained and that adverse events and protocol violations are reported to the Partners IRB as required.

10.4.5 E-Health App Privacy and Security

See Appendix 4 for the specifications related to the e-Health App which will be used for this study.

10.5 Adverse Experiences Monitoring and Reporting

An adverse event (AE) is any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with a study, use of a drug product or device whether or not considered related to the drug product or device.

The adverse event (AE) definitions and reporting procedures provided in this protocol comply with all applicable U.S. FDA and ICH guidelines and regulations. The Principal Investigator will carefully monitor each subject throughout the study for possible adverse events. All AEs will be documented on eCRFs designed specifically for this purpose. It is also important to report all AEs, especially those that result in permanent discontinuation of the investigational drug being studied, whether serious or non-serious.

Subjects will be monitored for adverse events from the time they sign consent until completion of their participation in the study. For the purposes of this study, symptoms of progression/worsening of ALS, PD and HD including 'normal' progression, will not be recorded as adverse events. Relationship of adverse experiences to the experimental intervention will be assessed at each in-person and telephone study visit by recording all voluntary complaints of subjects and by assessment of the medical. Attention will be directed to clinical adverse experiences associated with the prior hypercaloric dietary intervention, as well as any evidence of unexpected worsening of the underlying disease. Laboratory surveillance tests will be obtained as outlined above.

A serious adverse event is defined as an adverse event that meets any of the following criteria:

- Results in death

- Is life threatening: that is, poses an immediate risk of death as the event occurred
This serious criterion applies if the study subject, in the view of the Site Investigator, is at substantial risk of dying from the AE as it occurs. It does not apply if an AE hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization.
Hospitalization for an elective procedure (including planned tracheostomy) or a routinely scheduled treatment is not an SAE by this criterion because a "procedure" or a "treatment" is not an untoward medical occurrence.

- Results in persistent or significant disability or incapacity
This serious criterion applies if the "disability" caused by the reported AE results in a substantial disruption of the subjects' ability to carry out normal life functions.

- Results in congenital anomaly or birth defect in the offspring of the subject (whether the subject is male or female)

- Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

An event is considered "life-threatening" if it places the subject, in the view of the Investigator, at immediate risk of death from the reaction as it occurred; i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may also be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one

of the outcomes listed in this definition. Examples of such medical events include blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

An inpatient hospital admission in the absence of a precipitating, treatment-emergent, clinical adverse event may meet criteria for "seriousness" but is not an adverse experience, and will therefore, not be considered an SAE. An example of this would include a social admission (subject admitted for other reasons than medical, e.g., lives far from the hospital, has no place to sleep).

An unexpected adverse event is any adverse event, the specificity or severity of which is not consistent with expected risks of the study intervention.

All unexpected and related SAEs will be reported to the Partners IRB within 24 hours of being aware of the event. Death due to progression of disease, as expected in ALS, will not be reported in an expedited manner except in cases where the outcome of death is deemed related to study treatment.

There will be ongoing monitoring of non-serious Adverse Experiences. All AEs will be summarized and reported to the Medical Monitor on a monthly basis.

10.5.1 Evaluating and Recording of Adverse Events

At each visit all adverse events that are observed, elicited by the Principal Investigator, or reported by the subject will be recorded in the appropriate section of the Adverse Event log, entered into the EDC and evaluated by the Principal Investigator.

Adverse events will be categorized according to the MedDRA coding system. This is a descriptive terminology, organized by body system and including specific criteria for grading severity of Adverse Events. This system will allow study coordinators to quickly search for the most relevant term for each event and will give specific criteria governing the reporting of severity for each term. With this system, the event will be coded at the site and subsequently checked by the Data Manager.

Minimum information required for each AE includes type of event, duration (start and end dates), severity, seriousness, causality to study intervention, action taken, and outcome.

The relationship of the AE to the study intervention should be specified by the Site Investigator, using the following definitions:

1. Not Related: Concomitant illness, accident or event with no reasonable association with treatment.
2. Unlikely: The reaction has little or no temporal sequence from administration of the study intervention, and/or a more likely alternative etiology exists.
3. Possibly Related: The reaction follows a reasonably temporal sequence from administration of the intervention and follows a known response pattern to the suspected intervention; the reaction could have been produced by the study

intervention or could have been produced by the volunteer's clinical state or by other modes of therapy administered to the volunteer.

4. Probably Related: The reaction follows a reasonable temporal sequence from administration of study intervention; is confirmed by discontinuation of the study intervention or by rechallenge; and cannot be reasonably explained by the known characteristics of the volunteer's clinical state.
5. Definitely Related: The reaction follows a reasonable temporal sequence from administration of study medication; that follows a known or expected response pattern to the study medication; and that is confirmed by improvement on stopping or reducing the dosage of the study medication, and reappearance of the reaction on repeated exposure.

If discernible at the time of completing the AE log entry, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Site Investigator and recorded on the AE log. However, if an observed or reported sign, symptom, or clinically significant laboratory anomaly is not considered by the Site Investigator to be a component of a specific disease or syndrome, then it should be recorded as a separate AE on the AE log. Clinically significant laboratory abnormalities are those that are identified as such by the Site Investigator and/or those that require intervention. The only exception to this will be disease progression symptoms as previously noted.

11 HUMAN SUBJECTS

11.1 Institutional Review Board (IRB) Review and Informed Consent

The PI will obtain approval from the Partners Human Research Committee (HRC, or Partners IRB) of this protocol and consent form. Signed consent will be obtained from each subject. 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 subject, and this will be documented.

The PI and all key personnel involved in the study will have completed the Collaborative IRB training initiative, a mandatory tutorial on the responsible conduct of human subject research, or will have completed a comparable, institution-approved tutorial regarding the protection of human subjects. An independent Medical Monitor will review the study data for safety concerns. The PI will be responsible to report adverse events experienced by study subjects to the MGH IRB, the Medical Monitor, and if requested the study sponsor.

11.2 Subject Confidentiality

Confidentiality will be maintained, as all subject research data will be coded with GUID number and initials. Blood samples for research will be de-identified and labeled using the GUID, prior to storage. Participant files will be kept in a secure, double-locked area. The electronic database used during the trial will be secure. To date no breach of our security barriers has occurred, and we actively maintain a high level of security to assess the confidentiality of our databases. Only key personnel in this proposal will have access to the data and the codes. Subject results will never be discussed in any form in the presence of other subjects in the study or with non-laboratory personnel. A subject will be referred to by his/her GUID number only. The PI, Steering Committee, and independent Medical Monitor will monitor privacy and confidentiality throughout the study.

11.3 Inclusion of Women

The gender distribution for subjects with sporadic ALS is approximately 60% male and 40% female. The MGH patient population includes 53% men and 47% women. The gender distribution for PD is approximately 66% to 33% while the gender distribution in HD is 50% to 50%. Dr. Wills' own clinic population is approximately 60% female. The study goal is to recruit men and women with ALS, PD and HD in an approximately equal ratio. Advertising the study with several disease foundations and patient support groups will aid in the recruitment process and, in particular, with the recruitment of female subjects.

11.4 Inclusion of Minorities

Potential study subjects will not be excluded from this study for reasons of race or gender and efforts will be made to enroll in representative numbers with respect to both gender and race. In particular, no racial discrimination will be made in subject enrollment. The participation of minority subjects will be actively encouraged throughout the study.

11.5 Study Modification/Discontinuation

The study may be modified or discontinued at any time by the IRB (or Human Research Committee), the study sponsor, the Office for Human Research Protections (OHRP), or other government agencies as part of their duties to ensure that subjects are protected.

12 PUBLICATION OF RESEARCH FINDINGS

Dr. Wills will be responsible for publications of results from this trial and will comply with NINDS guidelines on publication of NIH funded clinical trials. Her responsibilities will include the following:

- ☐ Analyze and interpret data gathered in this study, and write publications from these data.
- ☐ Submit manuscripts to selected journals and address peer reviewers' comments.
- ☐ Submit abstracts to selected meetings and present data at the meetings.
- ☐ Determine authorship on the basis of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors,1997).

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