

Nutritional counseling with or without mobile health technology: a randomized open-label standard-of-care-controlled trial in ALS

Anne-Marie M Wills (✉ awills@mgh.harvard.edu)

Massachusetts General Hospital <https://orcid.org/0000-0002-0901-4711>

Jamie Garry

Massachusetts General Hospital

Jane Hubbard

Massachusetts General Hospital

Taylor Mezoian

Massachusetts General Hospital

Christopher T Breen

Massachusetts General Hospital

Courtney Ortiz Miller

Massachusetts General Hospital

Paige Nalipinski

Massachusetts General Hospital

Stacey Sullivan

Massachusetts General Hospital

James D Berry

Massachusetts General Hospital

Merit Cudkowicz

Massachusetts General Hospital

Sabrina Paganoni

Massachusetts General Hospital

James Chan

Massachusetts General Hospital

Eric A Macklin

Massachusetts General Hospital

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Abstract

Background: Nutritional status is an important prognostic factor in Amyotrophic Lateral Sclerosis (ALS). We wished to study the safety, tolerability and efficacy of nutritional counseling with or without an mHealth application to maintain or increase body weight in ALS, compared to standard care.

Methods: In this randomized open-label, standard-of-care-controlled, single-center clinical trial, we randomly assigned adults with ALS to one of three nutritional interventions: counseling by their physician or nurse (“standard care”), counseling by a registered dietitian (RD) (“in-person”), or counseling supported by a mHealth app (“mHealth”). Both intervention arms received tailored nutrition recommendations and recorded dietary intake and weight biweekly (mHealth) or monthly (in-person). The primary outcome of weight and secondary and tertiary outcomes of calorie intake, ALSFRS-R, and quality of life (QOL) were recorded at each clinic visit and analyzed in an ITT mixed model analysis.

Results: A total of 88 participants were enrolled of whom 78 were included in this analysis. The three arms were well-balanced except for excess males in the mHealth arm and greater weight lost at baseline in the in-person arm. Participants in the mHealth arm increased their calorie intake at month 3 to an average of 94% (95% CI: 85, 103) of recommended calories, compared to 81% (95% CI: 72, 91, $p=0.06$ vs. mHealth) in the standard care arm. After 6 months, calorie intake and change in weight was not different among the three arms. QOL scores in the mHealth arm were stable over three months (0.3 points, 95% CI: -1.7, 2.2) compared to worsening in standard care (-2.1 points, 95% CI: -4.0, -0.2, $p=0.09$ vs. mHealth), but all scores declined by six months. ALSFRS-R total scores declined by an average of -2.6 points (95% CI: -5.1, -0.1) over six months in the mHealth arm ($p=0.13$ vs. standard care) compared to -5.8 points (95% CI: -8.2, -3.4, $p=0.74$ vs. standard care) in the in-person and -5.2 points (95% CI: -7.6, -2.9) in the standard care arm.

Conclusions: Nutritional counseling is safe but did not increase weight compared to standard care in ALS patients.

Trial Registration: Clinicaltrials.gov identifier NCT02418546. Registered April 16, 2015.

Keywords: Amyotrophic Lateral Sclerosis, ALS, Neurodegenerative disease, mobile health technology, mHealth, nutrition, nutritional counseling, randomized controlled trial

Background

Weight loss is a common symptom of ALS and can occur even before diagnosis [1-3]. Weight loss in ALS is likely due to multiple factors including dysphagia, depression, loss of appetite, difficulty manipulating utensils, and increased energy expenditure due to a hypermetabolic state [4-6]. After diagnosis, body mass index (BMI) is highly correlated with survival [7-9], and moderate obesity has been associated with

slower disease progression and longer survival [9, 10]. Weight loss has also been correlated with more rapid disease progression [1, 3], although causation remains uncertain.

We hypothesized that a nutrition intervention to maintain or increase body weight would improve survival in patients with ALS. We previously conducted a phase II multi-center, double-blind, placebo-controlled clinical trial of hypercaloric diets in participants who were receiving percutaneous enteral nutrition [11]. While the study size was small, participants randomized to the high carbohydrate/hypercaloric diet arm experienced significantly fewer adverse events including death (log-rank $p=0.03$). The ALSFRS-R score also declined by -1.07 (95% CI: $-1.71, -0.42$) points per month in the high carbohydrate/hypercaloric arm compared to -2.17 (95% CI: $-3.24, -1.10$) points per month in the control arm ($p=0.07$) [11].

Here we follow up this result with a clinical trial of hypercaloric nutrition for patients at an earlier stage of the disease. Oral supplements have been tested in two small clinical trials [12, 13] and are being tested in two ongoing larger studies [14]; however, it is not clear whether oral supplements increase the total calories consumed [15]. Instead, we chose to study the effects of nutritional counseling on dietary intake, weight, and disease progression. Nutritional counseling has been studied in one non-randomized [16] and one small randomized trial of limited nutritional counseling [17], with no difference in the rate of BMI decline over 3 months. Nutrition-based mHealth applications are easy to use, commonly available, and can facilitate frequent reminders and measurements [18, 19]. We designed a pragmatic study of nutritional counseling by a registered dietitian with and without the support of an mHealth app compared to standard nutritional counseling by a nurse or physician within an ALS clinic.

Methods

Study Design and Oversight

The electronic health application to measure outcomes remotely (EAT MORE) clinical trial was an investigator-initiated, phase II, prospective, open-label, standard-of-care-controlled, randomized, single-center clinical trial. The primary aims of the study were to test the feasibility, safety, tolerability and efficacy of a mHealth application to maintain or increase body weight compared to in-person nutritional counseling and compared to standard of care.

Participants

From May 2015 to July 2017, adults with ALS were recruited from the Massachusetts General Hospital (MGH) ALS multidisciplinary clinic. For participants' convenience, and to enable generalizability of the results, all study activities were performed at the time of routine clinic visits. All participants provided informed consent prior to screening procedures. At screening, eligible participants had to have a diagnosis of possible, probable, laboratory-supported probable or definite ALS using the revised El Escorial criteria [20], and pass the MGH swallowing screening tool (MGH-SST)[21] with a swallow screening score of 5 or greater. The exclusion criteria included a history of diabetes or BMI greater than

30 kg/m² with a history of cardiovascular disease (for full Inclusion/Exclusion criteria, see Supplementary Table 1).

Randomization and Masking

Participants were randomized 1:1:1 to one of three interventions: counseling by their physician and nurse (standard care) vs. nutritional counseling at each clinic visit (in-person) by a registered dietitian, vs. nutritional counseling supported by an mHealth application. The randomization schedule was developed by the MGH Biostatistics Center in permuted blocks of three. Due to the type of intervention, blinding of participants and researchers was not possible.

Interventions

All participants met with a registered dietitian at their baseline visit to collect their weight and dietary history using a 24-hour recall. Baseline calorie intake was calculated by analyzing the 24-hour recall using the Nutrition Data Systems for Research (NDS-R, version 2014) [22]. Caloric recommendations for the two intervention arms were calculated using the ALS Calorie Calculator by Kasarskis et al [23] modified by an additional 117.5-235 kcal/day depending on baseline BMI and weight history (See Supplementary Table 2) with the goal of gaining approximately 0.5-1 kg/month. Participants in the standard care arm received general counseling on balanced nutrition and weight maintenance but did not receive specific dietary goals. Participants in the mHealth arm were prescribed dietary goals through an mhealth app (NuPlanit, Boston, MA) available on iOS devices (iPhone or iPad). If participants did not have an iOS device, they were provided an iPad for the duration of the trial. Participants were instructed to complete 4 days of electronic food records and two home weights every 2 weeks. Participants could use the app more than the minimum requirement. Based upon participants' weight gain or loss during the study, a research RD with access to app data could modify their dietary recommendations empirically. Participants in the in-person nutritional counseling arm received written goals for calorie intake and the treating RD contacted participants at least monthly to ask them to complete paper food records and to weigh themselves at home. The total duration of the nutrition intervention was 6 months +/-1 month depending on when participants returned for their scheduled clinic appointments. If participants agreed to long-term follow-up, vital status was verified at the end of the study.

Results

Study Population

Eighty-eight people with ALS were screened and 80 participants were randomized. Eight participants were excluded at screening, primarily due to failing the swallow evaluation (Consort diagram, **Figure 1: Enrollment and Outcomes**). Two participants were later excluded from the analysis due to a change in diagnosis from ALS. Baseline demographics and disease characteristics were well-balanced across the three arms (**Table 1**) although participants in the mHealth arm were more likely to be male and

participants in the in-person arm had experienced greater weight loss before enrolling in the study. The low number of participants with bulbar onset in all groups was due to the screening swallow evaluation.

Primary Efficacy Outcomes

Eleven percent of participants did not return to the ALS clinic at 3 months and 27% did not return at 6 months, including participants who performed televisits only (see Figure 1). Alternative sources of data (other hospital and clinic visits) were used to reduce missing 6-month weight data to 23% in the mHealth arm, 27% in the in-person arm and 12% in the standard care arm. Participants in the mHealth arm initially gained an average of 0.3 kg (95% CI: -1.1, 1.8) at 3 months before losing on average -0.2 kg (95% CI: -2.4, 2.1) by 6 months. Participants in the in-person dietary counseling arm lost on average -0.1 kg (95% CI: -2.1, 2.0) by 6 months. Participants in the standard care arm lost roughly 1 kg more by 6 months (-1.2 kg, 95% CI: -3.2, 0.7) but did not differ statistically from either intervention ($p=0.5$ and 0.4 , respectively; **Figure 2A** and **Table 2**).

Secondary Efficacy Outcomes

Due to low completion rates for 4-day food records, we used 24-hour recalls to measure caloric intake in the three arms. At 3 months, participants in the mHealth arm consumed on average 344 Kcal/day (95% CI: -118, 805) more than controls ($p=0.14$) and participants in the in-person arm consumed on average 286 Kcal/day (95% CI: -160, 731) more than controls ($p=0.2$) (Table 2, Supplementary Figure 1D). Participants in the mHealth and in-person arms experienced similar changes from baseline in macronutrient intake relative to standard care (Supplementary Figure 1).

Tertiary Efficacy Outcomes

While the study was not powered to detect a difference in disease progression, participants in the mHealth arm declined by an average of -2.6 points (95% CI: -5.1, -0.1) on the ALSFRS-R over 6 months compared to -5.2 points (95% CI: -7.6, -2.9) in the standard care arm ($p=0.13$; **Figure 3A**). Participants in the in-person arm also declined by an average of -5.8 points (95% CI: -8.2, -3.4) over 6 months ($p=0.7$ compared to standard care). Change in weight over 6 months was strongly correlated to the change in ALSFRS-R with a Pearson correlation of $r = 0.46$ ($p<0.001$), with greater weight gain associated with slower rates of disease progression.

The 3-month PROMIS QOL scores improved in the mHealth arm by 0.3 units (95% CI: -1.7, 2.2) while worsening in the standard care arm by -2.1 units (95% CI: -4.0, -0.2; $p=0.09$; **Figure 3B**). The scores also worsened in the in-person arm by -1.0 units at month 3 (95% CI: -2.9, 0.8, $p=0.4$ compared to standard care arm). QOL worsened by month 6 for all participants and were not significantly different among the arms ($p>0.5$).

Safety and Tolerability Outcomes

There were no deaths in the mHealth arm, 1 death in the standard care and 4 deaths in the in-person dietary counseling arm (NS; Supplementary Figure 2A). None of the deaths were considered related to the study intervention. Time to placement of a gastrostomy tube was not different between study arms (Supplementary Figure 2B).

Adverse events are shown in Supplementary Table 3. One participant in the mHealth arm experienced an elevated HgbA1c (7.1%) and had a lacunar stroke after 4 months on the study intervention. There were no other reports of diabetes, stroke, or heart disease during the study.

Tolerability

In the mHealth arm, 77% of participants entered data into the app and 50% of participants used the app for more than 3 months (Supplementary Figure 3). In the in-person arm, 79% of participants engaged with the RD outside of clinic (telephone or email), and 50% maintained at least monthly communication for 6-months. Thus, both interventions failed to meet our *a priori* criteria for tolerability (compliance with at least 80% of counseling sessions over 6 months). Nutritional counseling was declined by 8% of participants in both intervention arms at month 3 and by 12% of the mHealth and 15% of the in-person participants at month 6. Non-compliance with nutritional counseling did not affect collection of weight or ALSFRS-R as these were collected as part of routine clinical care.

Compliance with Counseling

At baseline, the average estimated calorie intake for all participants was 82% (95% CI: 77%, 87%) of their calculated caloric needs. Participants in the mHealth arm increased their intake to an average of 94% (95% CI: 85%, 103%) of recommended calories at month 3, compared to 89% (95% CI: 80%, 98%) in the in-person arm and 81% (95% CI: 72%, 91%) in the standard care arm ($p=0.06$ for the difference between mHealth and standard care, **Figure 2B**). By month 6, calorie intake declined in all three arms.

Discussion

ALS participants randomized to nutritional counseling with frequent reinforcement by a mobile health app increased their dietary intake and percent of recommended calories compared with participants who received standard of care treatment. While this did not significantly increase weight, the rate of disease progression over 6 months as measured by ALSFRS-R total score was half as fast among mHealth participants compared to participants in the standard care arm. While reverse causation cannot be ruled out, the strong correlation between weight change and change in ALSFRS-R is consistent with our hypothesis that nutritional interventions could be effective in slowing progression of ALS.

The lack of a statistical difference in weight change in either intervention arm may reflect low power due to the smaller than planned sample size and the limited weight loss observed in the standard care arm. Physicians and nurses in our clinic now routinely counsel all ALS patients to avoid weight loss, which may have contaminated our study results. It is interesting that an increase in dietary intake during the

first 3 months of the intervention did not translate into a significant increase in weight over the same time period. This may be due to the hypermetabolic nature of the disease or due to the short duration of participant engagement in both arms.

Lack of adherence is a common issue with behavioral interventions and mhealth applications in particular, with a reported retention rate for mhealth apps as low as 30% (reviewed in [28],[29]). This may explain, in part, the disappointing results of mhealth apps for treating obesity (reviewed in [28]). It is possible that mhealth apps that engage participants for longer periods would achieve greater weight gain and might slow disease progression more effectively.

The lack of efficacy of nutritional counseling alone was surprising and could be due to several factors. First, nutrition counseling sessions were often shortened or canceled to accommodate other multidisciplinary care providers. Second, participants in the mHealth arm were reminded more frequently and had the opportunity to interact with the app more frequently (daily, if desired). Third, participants assigned to the in-person arm had experienced greater weight loss prior to enrollment in the study, although our analyses adjusted for change in BMI prior to enrollment.

There are several limitations to this study. First, the intervention could not be blinded due to the study design; however, the outcomes (weight and ALSFRS-R) were collected in the clinic by staff who were not involved in randomization and were unlikely to be biased by knowledge of study arm allocation. Second, the trial was performed at a single institution, which limits the generalizability of these results. One positive aspect of our single-site design was that the interventions were uniformly administered by the same team of dietitians. A third limitation was the substantial drop-out by month 6. Nevertheless, while participants did not always comply with collection of dietary data, weight and ALSFRS-R were collected as part of routine clinical care, providing more complete outcomes data.

One strength of our study was the enrollment of many participants who would not have qualified for typical ALS clinical trials, including more advanced participants, improving the generalizability of our results. Moreover, our pragmatic study design allowed us to test the real-world effect of having a registered dietitian assigned to the clinic, with realistic follow-up outside the clinic. Our results suggest that more frequent engagement is necessary to achieve dietary goals.

Our results support the use of this non-pharmacologic treatment for people with ALS. These results are consistent with our prior study which demonstrated that hypercaloric enteral nutrition was associated with improved survival and slower progression. The strong correlation between weight gain and slower ALSFRS-R progression in our study are consistent with the epidemiologic and pre-clinical data. While further study is needed, given the low risk and likely benefit of using an mHealth app to increase calorie intake in ALS, we believe that these methods should be made widely available to people with ALS to help maintain weight.

Abbreviations

ALS=Amyotrophic Lateral Sclerosis; ALSFRS-R= Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; CONSORT= Consolidated Standards of Reporting Trials; ITT= Intention to treat; MGH= Massachusetts General Hospital; mHealth= mobile Health; NDS-R= Nutrition Data Systems for Research; PROMIS= Patient Reported Outcomes Measurement Information System; RD= Registered Dietitian; QOL= Quality of Life

Declarations

Ethics approval and consent to participate:

The protocol and consent forms were approved by the Partners Human Research Committee. All procedures followed were in accordance with the ethical standards of the responsible institutional or regional committee on human experimentation or in accordance with the Helsinki Declaration of 1975, as revised in 1983.

Consent for publication:

N/A

Availability of data and material:

The datasets used and/or analyzed during the current study are available from the corresponding author on request and will be added to the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) Database (<https://nctu.partners.org/proact/data/index>). The full protocol, statistical analysis plan and CONSORT checklist for trials of nonpharmacologic treatments are available as supplementary materials.

Competing Interests:

Anne-Marie Wills M.D., M.P.H. has received research funding from the ALS Association, has participated in clinical trials funded by Acorda, Biogen, Bristol-Myers Squibb, Sanofi/Genzyme, Pfizer and received consultant payments from Acorda, Accordant, a CVS/Caremark disease management company.

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James Chan MA

Eric A. Macklin PhD serves on Data and Safety Monitoring Boards for Acorda Therapeutics and Shire Human Genetic Therapies, received research funds and served on a Steering Committee for Acorda Therapeutics, and consulted for Myolex Inc. and Lavin Consulting.

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Authors' Contributions:

AMW, JG, JH, and EM designed the research study; AMW, JG, JH, MC, TM, CB, CM-O, PN, SS, JB, and SP conducted the research; AMW, JH, JG, JC and EM analyzed the data; AMW, JG, JH, JB, SP, JC and EM wrote the paper; AMW had primary responsibility for final content and for the decision to submit the manuscript.; All authors read and approved the final manuscript.

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Tables

Table 1. Baseline Characteristics of Participants ¹

	Standard Care	In-person	mHealth	Overall p-
	N=26	N=26	N=26	value
Male N(%)	11 (42.3%)	16 (61.5%)	20 (76.9%)	0.04
Age (mean±SD yrs)	57.5±10.9	58.5±11.9	54.7±11.5	0.47
White Not-Hispanic N(%)	24 (92.3%)	25 (96.2%)	25 (96.2%)	0.77
Bulbar Onset N(%)	3 (11.5%)	2 (7.7%)	4 (15.4%)	0.69
ALSFRS-R (mean±SD)	36.7±5.4	34.9±6.7	37.4±6.2	0.35
Months since symptom onset (mean±SD)	22.3 (18.0)	26.1 (16.8)	27.1 (18.9)	0.60
BMI (mean±SD kg/m²)	26.8±5.1	25.7±4.1	26.0±4.5	0.70
Weight loss since diagnosis (mean ±SD kg)	3.4±5.5	6.3±7.1	2.1±3.4	0.03
Weight loss since max weight (mean ±SD kg)	7.8±9.4	10.4±10.7	6.0±6.7	0.23
Change in BMI since diagnosis (mean±SD kg/m²)	1.2 ±1.9	2.2 ±2.6	0.6 ±1.0	0.01

¹ Baseline characteristics of participants are shown according to treatment group in frequency (N) and percent or mean and standard deviation (SD); Bulbar onset= symptoms of ALS beginning in the cranial nerves; ALSFRS-R= ALS Functional Rating Scale-Revised; BMI= body mass index.

Table 2. Change over Time in Outcomes by Treatment

P-values

Group ¹

	Standard Care	In-person	mHealth	In-person vs SC	mHealth vs SC
Change in ALSFRS-R at month 3	-1.9 (-3.4, -0.3)	-2.1 (-3.8, -0.5)	-2.0 (-3.8, -0.3)	0.80	0.88
Change in ALSFRS-R at month 6	-5.2 (-7.6, -2.9)	-5.8 (-8.2, -3.4)	-2.6 (-5.1, -0.1)	0.74	0.13
Change in PROMIS QOL at month 3	-2.1 (-4.0, -0.2)	-1.0 (-2.9, 0.8)	0.3 (-1.7, 2.2)	0.42	0.08
Change in PROMIS QOL at month 6	-2.8 (-5.2, -0.5)	-2.3 (-4.6, -0.1)	-1.9 (-4.4, 0.5)	0.77	0.59
Change in Weight at month 3 (kg)	-0.0 (-1.4, 1.3)	-0.1 (-1.5, 1.3)	0.3 (-1.1, 1.8)	0.95	0.70
Change in Weight at month 6 (kg)	-1.2 (-3.2, 0.7)	-0.1 (-2.1, 2.0)	-0.2 (-2.4, 2.1)	0.41	0.47
Change in % Calories at month 3	-0.6 (-10.4, 9.2)	6.8 (-2.5, 16.0)	12.2 (2.5, 21.8)	0.26	0.06
Change in % Calories at month 6	3.5 (-7.9, 14.9)	7.6 (-3.9, 19.2)	1.0 (-10.7, 12.6)	0.59	0.75
Change in total kCal at month 3	-35.3 (-368.8, 298.1)	250.3 (-65.2, 565.8)	308.2 (-21.2, 637.6)	0.21	0.14
Change in total kCal at month 6	83.9 (-298.7, 466.4)	78.2 (-295.5, 451.8)	-33.7 (-424.5, 357.1)	0.98	0.66

¹ Change over time from baseline according to treatment group, adjusted for sex and change in BMI from diagnosis to baseline. Parameter estimates of change from baseline and 95% confidence intervals are shown. ALSFRS-R is shown in units, PROMIS sf v1.1 is shown in units, higher scores are better. Change in % Calories= change in self-reported

calories consumed as a percent of recommended calories according to the Kasarskis equation [23]; SC=Standard Care.

Figures

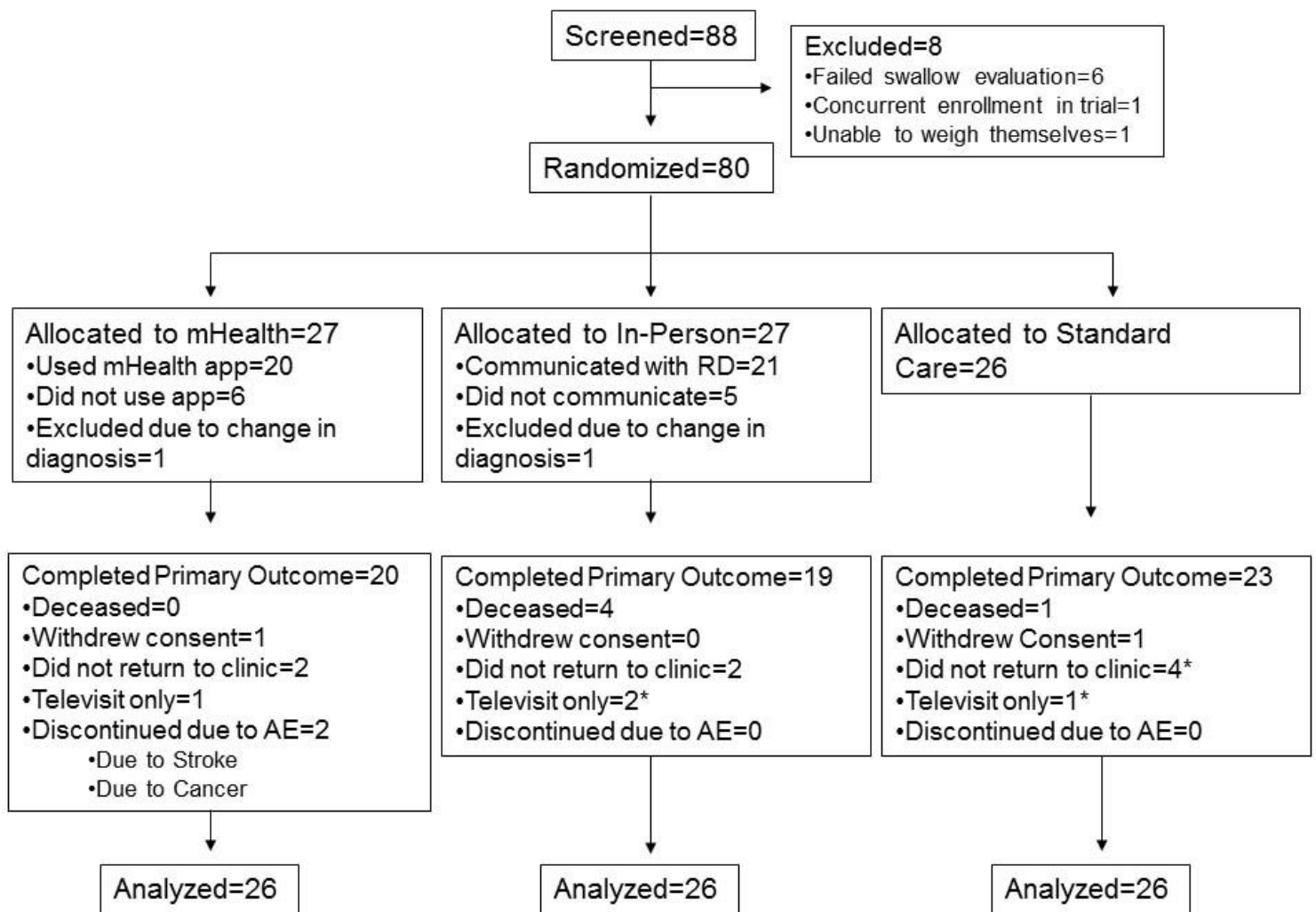


Figure 1

Consort Flow Diagram - Consort flow diagram showing the final disposition of participants in the study. Participants who did not return to the clinic for their month 6 visit but who supplied weight data for the primary analysis are marked with an asterisk.

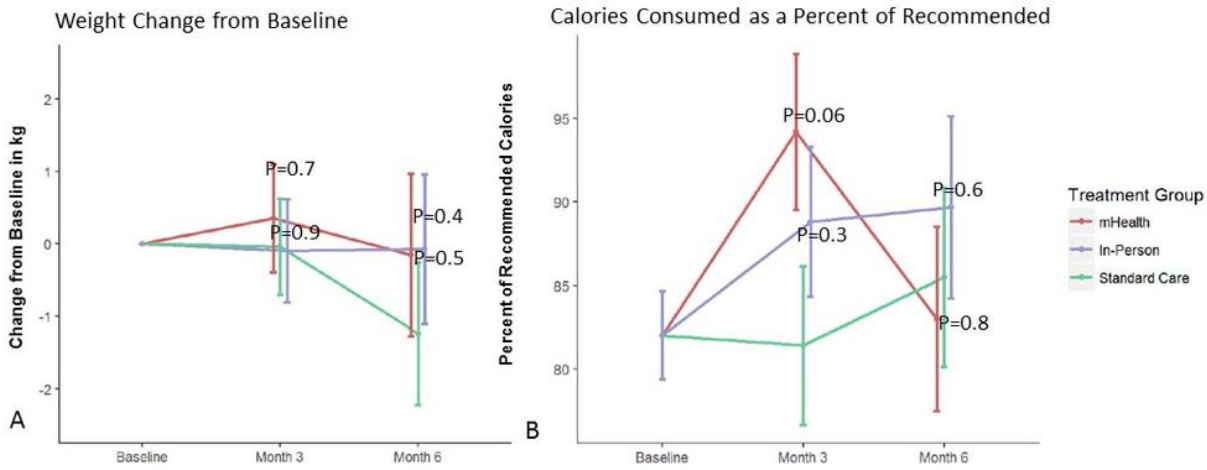


Figure 2

Change in weight and calories consumed by intervention group - Figure 2A: Change in weight from baseline by intervention group using measured clinic weights. Figure 2B: Calories consumed as a percent of calculated dietary requirements by intervention group at each visit. Red= mHealth; Blue= In-person dietary counseling; Green= Standard Care. Error bars represent 1 standard error around the mean.

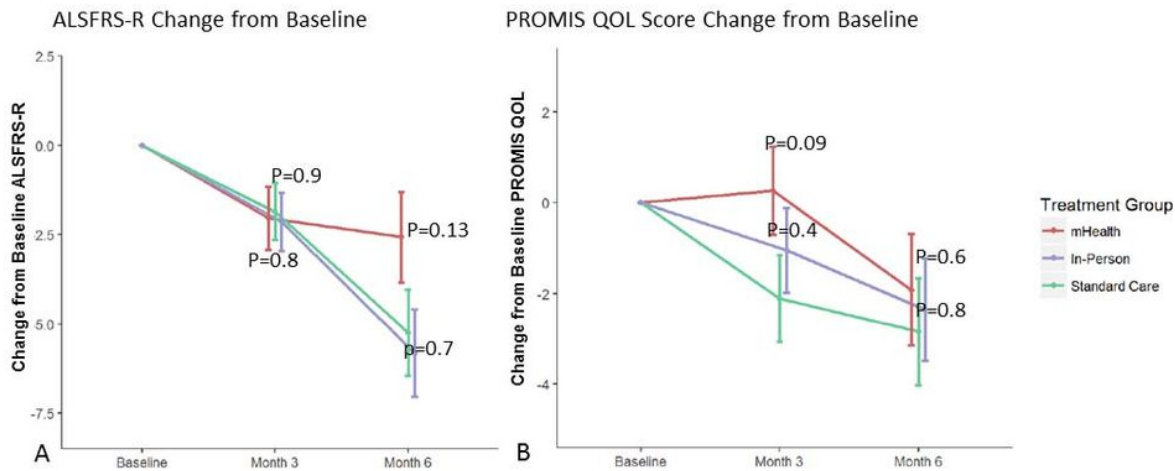


Figure 3

Change in ALSFRS-R and QOL by intervention group - Figure 3A: Change in ALSFRS-R from baseline by intervention group. Figure 3B: PROMIS SF v 1.1 Global Health QOL scores by intervention group and visit (higher scores are better). Red= mHealth; Blue= In-person dietary counseling; Green= Standard Care. Error bars represent 1 standard error around the mean.

Supplementary Files

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