Study Protocol and Statistical Analysis Plan (SAP)

MULTI-CENTER RANDOMIZED CONTROLLED TRIAL OF REFEEDING IN ANOREXIA NERVOSA:
The Study of Refeeding to Optimize iNpatient Gains (StRONG)

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Abbreviations

AAN	Atypical anorexia nervosa
AN	Anorexia nervosa
DCC	Data Coordination Center
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, fifth edition
EDE	Eating Disorder Examination
EDE-Q	Eating Disorder Examination-Questionnaire
HCR	Higher Calorie Refeeding
kcal	Calories
LCR	Lower Calorie Refeeding
mBMI	median Body Mass Index (for age and sex)
SOC	Standard of Care

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PROTOCOL Version 1.3 (See Table of Amendments)

Multi-Center Randomized Controlled Trial of Refeeding in Anorexia Nervosa

1. Introduction

Current recommendations to guide the clinical care of AN patients hospitalized with medical instability due to malnutrition are based solely on retrospective or observational studies and/or clinical experience. No studies to date have prospectively tested high calorie refeeding (HCR) and the long-term impact on recovery is unknown. Consensus has developed over recent decades that patient safety can only be guaranteed using low calorie refeeding (LCR). The entrenchment of clinical practice without supporting evidence is a widely recognized dilemma in healthcare. While RCTs are considered the "gold standard" to establish evidence-based medicine, until recently there was insufficient data to propose such a study of refeeding in AN. We now have preliminary findings to indicate that LCR might be too cautious and that HCR appears feasible and may improve long-term recovery. Thus, we are poised to compare these two treatments in a parallel, randomized fashion.

2. Study Design

The purpose of this multi-center randomized controlled trial is to compare LCR vs. HCR refeeding strategies for hospitalized adolescents with AN. Participants will be recruited upon hospital admission at two centers (UCSF and Stanford) to maximize sample size, and randomly assigned 1:1 within site to one of the two strategies. A total of 120 participants age 12-24 yrs who meet DSM-5 diagnostic criteria for AN and atypical AN and present as medically unstable due to malnutrition will be enrolled. Treatments will not be blinded, since both the patients and clinicians who work with this population are highly skilled at estimating kcal and would be able to determine their group assignment by simply viewing the meal trays. In addition, target kcal will be reached faster in HCR and this would be apparent on physician orders. The proposed study is powered to detect a meaningful difference in clinical remission (Aim 1A).

2.1. Study Population

a. Inclusion/Exclusion: Adolescents hospitalized for medical instability secondary to malnutrition will be eligible as follows. Inclusion criteria: diagnosis of AN, atypical AN, age 12-24 years, no hospital admissions for the previous six months, and meet hospitalization criteria (daytime HR < 50 bpm or night time HR < 45 bpm, BP <90/45 mmHg, temperature < 35.6° C or orthostasis defined by increase in HR > 35 bpm or decrease in systolic BP > 20 mmHg from lying to standing). Exclusion criteria: diagnosis of bulimia nervosa [DSM-5], currently in remission (as defined by weight and EDE-Q score per Aim 1), admission for food refusal without malnutrition, current pregnancy, chronic disease (e.g. immune/endocrine disorders, pulmonary, cardiac, or renal disease), current suicidality or psychosis.

b. Participant recruitment and consent: Participants and their parents will sign assent (for those < 18 yr) and consent, respectively within 24 hr of hospitalization. This may occur in the clinic when they are deemed medically unstable and waiting transfer to the hospital or in the hospital if admitted directly. Consent will include permission to review all medical records, to review hospital billing data, and to contact for future research projects. If a participant turns 18 yr while enrolled, s/he will be reconsented. Participants 18 years of age and older are able to consent themselves; thus we will request verbal consent from their parents to complete parent surveys.

2.2. Randomization

Participants will be stratified by site and randomly assigned 1:1 to the two intervention strategies within 24 hr of hospital admission. The Data Coordination Center (DCC) will provide a secure unpredictable allocation sequence (e.g. A B B A …) which will be programmed into a secure electronic study tracking system for assignment of each accrued participant. The sequences will be generated using block size of two to four to maximize balance between arms throughout accrual while ensuring the sequences remain unpredictable. As patients consent to study participation, clinical-research staff will assign the next available study ID number in sequence, identify the allocated intervention arm, and inform participants and their families of the assignment. In turn, the clinical research staff will provide the linked study ID number and Medical Record Number to the DCC, which will store this Personal Health Information in a HIPAA-compliant manner along with the intervention assignment.

3. Study Procedures

3.1. Treatment and Follow-up

a. Study groups: Upon randomization, the Lower Calorie Refeeding (LCR) group will begin with 1400 kcal per day; Higher Calorie Refeeding (HCR) group will commence at 2000 kcal. Given our previous findings, recognition of the so-called underfeeding syndrome and recent clinical experience, we will not test a 1200 calorie diet even though it is still currently recommended. Our previous studies have adequately demonstrated that a 1200 kcal diet produces initial weight loss and therefore do not feel it is ethical to assign participants to this treatment. We chose 1400 kcal to start because in our previously study of LCR, weight loss ceased on day 3 in hospital when diets averaging 1411(299) kcal were prescribed. Diet prescriptions will increase by 200 kcal every other day in LCR and 200 kcal per day in HCR until a target level is reached. Target kcal are calculated upon admission as percent of energy needs using Estimated Energy Requirement (EER) equations from the Institute of Medicine. These equations are used clinically to set goals for caloric advancement although they are known to underestimate energy needs in patients with anorexia. Therefore, we maximize these estimations by using target weight corresponding to the mBMI for age and sex (rather than current weight), a moderate activity factor of 1.2-1.3 (despite bed rest), and additional 500 kcal (if current weight < the MBMI).

b. Intervention (refeeding protocols): During hospitalization, participants will follow a meal-based refeeding protocol that calls for eating three meals and three snacks per day, served on trays at the bedside, in the presence of 'Room Sitters'. The calorie level of the diet will be prescribed by the physicians per study protocol and the meals will be prepared by hospital foodservice. The study PI (Garber) will work with the Research Registered Dietitian (RD) and nutrition staff at both sites to ensure that menu selections fit the general macronutrient distribution of 30-40% fat, 15-25% protein and 35-55% carbohydrate. Menus will be continually analyzed (Software v.17.9.5, Computrition, Inc., Chatsworth, CA) to ensure conformance to this distribution as menu items are added or change over time. Dietetic Technicians will keep daily calorie counts, per Standard of Care (SOC), showing actual kcal consumed from food and formula.

   A high energy liquid supplement ("formula") providing 1.5 kcal per mL (360 kcal per 240 mL can) will be used orally as needed to replace kcal refused in meals or snacks per a standard calorie replacement protocol. We previously reported a greater than 98% concordance between kcal prescribed and actual kcal ingested using this method, as well as an equal proportion of kcal intake from formula in LCR and HCR groups. This finding supports our clinical observation that HCR meals can be completed without additional reliance on drinking formula. However, most AN patients do experience discomfort during refeeding and therefore all participants will receive SOC meal support including emotional support and techniques such as distraction. All beverages will be weighed and measured before placement on the tray, with a 1.5 L per day free water restriction. Room sitters will observe intake of all meals/snacks and remain in the room for 45 min afterwards.

c. Monitoring of electrolytes: Blood for electrolytes will be obtained between 5 and 7 am every 24hr for the first 7 days and more frequently if needed. Since the risk of refeeding decreases after the first week, electrolytes will be monitored every other day starting on day 8 unless there is continued evidence of abnormalities.

d. Correction of electrolyte abnormalities: Electrolyte abnormalities (serum phosphorus < 3 mg/dL, magnesium ≤ 1.7 mg/dL, or potassium < 3.5 mEq/L) will be corrected with a standardized protocol for both sites. Patients with hypophosphatemia will be treated with sodium potassium phosphate, 250 mg per packet (8 mmol phosphorus, 7.1 mEq potassium), one packet three times a day by mouth for a serum phosphorus between 2.5 and 2.9 mg/dL, two packets (500 mg) three times a day for a serum phosphorus of 2.0 - 2.5 mg/dL, and if serum phosphorus is < 2.0 mg/dL then intravenous sodium potassium phosphorus will be initiated at a dose of 0.24 mmol/kg (max of 15 mmol per dose). The PICU will be contacted and labs will be rechecked STAT 4 hours after the infusion is completed. Those with hypomagnesemia will be prescribed magnesium oxide (150 mg elemental Mg per tablet), one tablet three times a day by mouth for a serum magnesium between 1.3-1.7 mg/dL; two tablets three times a day by mouth for a serum magnesium between 1.0-1.2 mg/dL. In the case of serum magnesium below 1.0 mg/dL, the PICU will be called for possible transfer, and intravenous magnesium sulfate will be started at a dose of 50 mg/kg (max of 2 grams per dose). Labs will be rechecked STAT 2 hours after infusion completed: If repeat serum mag still < 1.0 mg/dL, repeat same dose of magnesium sulfate IV; If repeat serum mag > 1.0, begin PO Mag, at PO dose indicated above. Those with hypokalemia will be prescribed extended release potassium chloride by mouth, 20 mEq for a serum potassium of 3.1-3.4 mmol/L; and 40 mEq for a serum potassium of 2.5-3.0 mmol/L. For a serum potassium between 2.2 - 2.5 mmol/L, 40 mEq extended release potassium chloride will be given STAT and the PICU will be called for possible transfer. Labs will be rechecked in 4 hours (peak) and 12 hours (estimated nadir). For any serum value of potassium < 2.2 mmol/L, intravenous potassium chloride will be initated and PICU will be called for transfer. Declining electrolyte levels that are in the normal range will not be treated.
Participants will also receive a SOC supplement regimen including 500mg elemental calcium with vitamin D twice per day and an adult multivitamin with minerals once per day.

e. Study time points: Participants will be followed prospectively in hospital with daily measures of calorie and supplement intake and weight from admission through discharge. Patients will be discharged when medically stable, with the primary criterion of heart rate ≥ 45 bpm for least 24 hr. Full medical stability defined as HR ≥ 45 bpm for 24 hrs, temperature ≥ 35.6ºC for 24 hrs, ≥ 75% of mBMI, BP ≥ 90/45 mmHg for 24 hrs or if systolic BP < 90 then asymptomatic and all else stable, orthostatic change in HR ≤ 35 bpm or if > 35 then asymptomatic and all else stable; and orthostatic change in SBP ≤ 20 mmHg or if > 20 then asymptomatic and all else stable.

Timing of Procedures: Table 1

	INPATIENT			OUTPATIENT FOLLOW---UP				
	Admit	Daily	DC*	10 dy	1 Mo	3 Mo	6 Mo	12 Mo
MEDICINE/NURSING PROCEDURES								
Weight	SOC	SOC	SOC	X	X	X	X	X
Height	SOC			X	X	X	X	X
Vital Signs	SOC	SOC	SOC	X	X	X	X	X
Electrolyte monitoring ¥	SOC	X	SOC					
NUTRITION PROCEDURES								
24---hr food recall	X			X	X	X	X	X
QUESTIONNAIRE ADMINISTRATION								
EDE-Q	X		X		X	X	X	X
HCUMS survey				X	X	X	X	X
Demogr & Eating Disorder	X							

Follow---up form				X	X	X	X	X

* DC = discharge; SOC = Standard Of Care; Rnd = Randomization; ¥ SOC is every other day; we will monitor daily as part of Aim 2.

3.2. Data Collection

Other than the treatment we are testing (HCR vs. LCR), patients will receive SOC in the hospital. Thus, as shown in **Table 1**, the vast majority of procedures in hospital are SOC. Follow-up visits, on the other hand, are for the purpose of collecting data and will be scheduled at the designated time points.

a. **Baseline data collection:** The following covariates will be collected upon admission, prior to randomization.
   (1) Demographics and eating disorder history: an intake form will be self-administered (with study coordinator as proctor, 15 min) to assess: highest body weight, lowest body, date of onset (to calculate length of illness and rapidity of weight loss), family history of eating disorder, self-reported race/ethnicity, maternal education and zipcode (to indicate socioeconomic status), date of birth.
   (2) Eating Disorder Examination-Questionnaire (EDE-Q): is a standardized research interview that measures eating disorders psychopathology. Dr. Le Grange (co-I, UCSF) has used this tool extensively in RCTs examining psychotherapeutic modalities and long-term recovery in AN and BN and to categorize lower and higher risk study participants. He will oversee the psychological aspects of this study, including the EDE-Q.
   (3) Food recall: dietary intake for the day prior to hospital admission will be assessed with a 24-hr food recall by the Research RD and analyzed via Nutrition Data System for Research (NDS-R) for total kcal and macronutrient profile. Dietary Density (DDS) and Variety Scores (DVS) will be calculated since acceptance of more energy dense and variety of foods in hospital has been shown to predict recovery at 8 mo.
   (4) Severity of illness: %mBMI and HR on admission
   (5) Health Care Utilization and Missed School (HCUMS) Survey: This proctored interview draws from established tools to assess cost, and has been tailored for AN and integrated with the follow-up form (above). In addition to to "other care", it assesses health care utilization in the 6 months prior to admission including medications, physician visits, dental visits, ER visits and laboratory testing. It will be administered by trained research staff, who will document parent- and participant-reported care, supplemented with dates, doses, and other details available in the medical record.

b. **Data collection daily in Hospital:**

   (1) SOC in hospital: Participants will be followed daily in hospital. Consistent with SOC for these patients, night time HR will be assessed with continuous cardiac monitoring throughout hospital stay, temperature will be measured orally and BP will be measured every 4-8 hr. Postural changes will be assessed with supine measurements (after 5 min), followed by standing measurements (after 2 min). When multiple vital signs measures are taken per protocol during one hospital day or one outpatient clinic visit, the most deviant value (lowest HR, lowest BP, greatest increase in HR and greatest decrease in BP on orthostatic changes, lowest Temp) will be recorded. Weight is measured every morning upon waking after voiding on an electronic scale, with the subject wearing only a hospital gown. Height will be measured within 24 hours of admission with wall-mounted stadiometer. Electrolytes will be monitored per SOC as described above in 3.1.c.

   (2) Study in hospital: Participants at both sites will complete the questionnaires above.

c. **Data collection during follow-up:** Participants will return for five study follow-up visits through 12

months post-discharge and complete the following procedures:

(1) Anthropometrics and vital signs: Height, weight and vital signs will be measured according to the in-hospital protocol by trained medical staff with standard equipment. Vital sign measures will be taken after a 20-min rest to minimize the influence of activity required to attend the visit (e.g. walk from car). After resting, vital signs will be measured in the research center with standard, calibrated equipment and with postural changes according to the procedure above. Data will be entered directly into the electronic data capture system with fillable and constrained sections for anthropometric measures and vital signs to minimize error.

(2) Food recall: dietary intake for one full day during the week of each follow-up visit will be assessed with a 24-hr food recall by the Research Dietitian.

(3) HCUMS Survey: As described above, this proctored survey will assess utilization of health care such as re-hospitalizations since the time of the study-related hospitalization, participation in eating disorder treatment programs, medications, missed school, missed work, and other direct and indirect costs associated with eating disorder care since the time of each prior follow-up visit. The HCUMS will document medications pertinent to recovery measures (menses and psychopathology), including medications, current mental health care, other medical and psychological/psychiatric care ("other care") outside of our medical centers (e.g. residential care, psychiatric hospitalization). Psychotherapy modality and adherence may be important prognostic covariates of long-term outcomes in this open follow-up study.

3.3. Safety

This study begins with a hospitalization as per SOC for patients who are medically unstable with malnutrition secondary to AN. Patients will be admitted to the adolescent medicine service if they are deemed medically unstable per published criteria. Once admitted, patients will be eligible for study enrollment. The treatment (HCR or LCR) is limited to the hospital stay. Aside from the questionnaires at both sites and daily (instead of every other day) electrolyte monitoring, all hospital procedures are consistent with SOC. After discharge, participants will be followed openly. They are required to be under a physician's care to ensure medical stability but not required to receive that care from us (however many do). Many patients have a psychiatrist to manage psychiatric co-morbidities such as anxiety and depression. If they receive care or hospitalization elsewhere they can still continue in the study and we will collect that with our follow-up form**.**

a. Prospective monitoring of AEs: Aim 2 specifies three electrolyte abnormalities that will be monitored prospectively in all participants and documented as described in **3.1.c.&d.**: hypophosphatemia (<3 mg/dL), 2B) hypomagnesaemia (≤1.7 mg/dL), and 2C) hypokalemia (<3.5 mEq/L).

b. Data and Safety Monitoring Board (DSMB): As a multi-center clinical trial comparing treatments, the proposed study is required to have a DSMB according to the NICHD policy for clinical research monitoring. The purpose of the DSMB is to ensure the safety of participants and validity of the trial. We will draft a DSM Plan using the NICHD template.

STATISTICAL ANALYSIS PLAN (most recent change May 26, 2019)

Multi-Center Randomized Controlled Trial of Refeeding in Anorexia Nervosa

1. Aims and Objectives

Our study has three main aims. We will compare:

AIM 1: Efficacy of LCR vs. HCR. We hypothesize that LCR and HCR will differ by *achievement and maintenance of*: (1A) clinical remission during 12 mo follow-up, defined by achievement of both–(i) weight ≥ 95% median BMI (MBMI) for age and sex, and (ii) Eating Disorder Examination-Questionnaire (EDE-Q) global score within 1 SD of clinical norm, and (1B) medical stability during initial hospitalization, defined by published vital sign thresholds.

AIM 2: Safety of LCR vs. HCR during initial hospitalization. We hypothesize that LCR and HCR will *not* differ by *incidence of*: 2A) hypophosphatemia (<3 mg/dL), 2B) hypomagnesaemia (≤1.7 mg/dL), and 2C) hypokalemia (<3.5 mEq/L).

AIM 3: Cost-effectiveness (CE) of LCR vs. HCR. We hypothesize that HCR will be more cost-effective than LCR, as determined by cost (including costs of initial and re-hospitalizations, 12 mo follow-up, other care, and safety/adverse events (AEs) and effectiveness per adolescent recovered (defined in AIM 1A and B).

2. Statistical Methods

2.1. Pool of participants

a. Projected pool of eligible participants and accrual rate: At Stanford, in 2012 there were 295 admissions to the dedicated inpatient eating disorders unit, with approximately 36% of patients meeting DSM-4 criteria for AN; 100 similar patients were admitted at UCSF. With the broader eligibility criteria also including DSM-5, we anticipate at least 40% of patients (120 per yr at Stanford and 40 at UCSF) will be eligible. Of those who are eligible, we estimate that at least 50% will agree to participate and thus we will not attempt to achieve equal enrollment across sites. We will accrue 3-4 participants per mo over 3 yr until N=120 is reached and retain 85% of this sample through 12 mo as shown in open follow-up studies of participants with AN.

b. Commitments of Site PIs, Research Teams, and Participants: Both site PIs have successfully recruited and retained AN participants in research projects and seen them to completion and publication. Furthermore, co-I Cheng is a faculty biostatistician with extensive experience in clinical trials. She will lead the DCC, aiming to ensure the trial is designed, executed, and analyzed without bias. Patient incentives to participate will emphasize the value of their contributions to medical research and remuneration for their time.

c. Data Analyses:

Sample Description: The study sample will be summarized and described (e.g., mean ± SD) by stratification factor and baseline covariates to confirm general balance by arm and data will be summarized for completeness of follow-up (e.g., length of stay, last visit).

2.2. Outcomes

The primary analysis of the study adopts a modified intent-to-treat (mITT) approach to compare outcomes between randomized HCR and LCR participants who received treatment for at least one day. Patients who are ineligible post randomization, provide no assent after parent's consent, or withdraw before receiving any treatment, will not be included in the mITT analysis for reasons of data unavailability, ethics and clinical relevance. Sensitivity analyses will be conducted to check that 1) withdrawal patients are not different from patients in both groups included in mITT in baseline covariates; and 2) including withdrawal patients in the

analyses will not change results and conclusion of mITT analyses. The sensitivity analyses will provide us reassurance of mITT results.

Aim 1A: Primary (long-term) efficacy outcome. A (generalized) linear mixed-effects regression model (GLMM) will compare study arms with respect to achievement and maintenance of clinical remission. Clinical remission is defined as the combination of mBMI and EDE-Q score at mo 1,3,6,12 (separate analyses below) and measured at 1, 3, 6, and 12 months as 1) clinically remitted (yes or no) and 2) weight recovered (percent of mBMI). The models will include time, treatment group, time*treatment group interaction, and unbalanced baseline covariates if any as fixed effects, while sites and patients will be included as random effects to account for the correlation due to clustering. The time*treatment group interaction provides mITT effect of HCR compared to LCR on clinical remission over time. The average remission rates and scores and their 95% confidence intervals (CIs) will be estimated from the model. GLMM accounts for the fluctuating nature of mBMI and EDE-Q in AN and uses all available data with missing at random assumption, instead of a stronger assumption of missing completely at random required in other models. Aim 1 models will be supplemented with secondary analyses: (i) potential moderators at baseline (included in regression models as main effects and interactions with period and time), may include DSM-5 criteria and EDE-Q thresholds of risk and (ii) potential mediators at follow-up (included as time-dependent covariates), may include food recall (DDS and DVS), healthcare utilization, or incidence of AEs. In addition, separate mixed-effects models will analyze continuous versions of mBMI and EDE-Q to describe longitudinal trajectories.

Aim 1B: Secondary (short-term) efficacy outcome: Time to restore and maintain medical stability in hospital is defined as days to reverse the medical instability indicators for hospitalization in adolescents with eating disorders. A six-point index will adjudicate daily medical stability: 1.) 24-hour heart rate (HR) ≥ 45 bpm, 2.) systolic blood pressure (SBP) ≥ 90 mmHg, 3.) temperature ≥ 35.6° C, 4.) orthostatic increase in HR ≤ 35 bpm, 5.) orthostatic decrease in systolic BP ≤ 20 mmHg, and 6.) ≥ 75% of mBMI. Each of the six criteria were scored as "1" if met, "0" if unmet and missing (not scored) if not measured. Medical stability was considered restored when all criteria were stable for 24 hours, allowing a maximum of two missing values (i.e. participants were considered stable if meeting 4 of 4, 5 of 5 or 6 of 6 measured criteria). All randomized participants who receive at least one day of treatment, including those who withdraw at any time during the refeeding intervention, will be included in the mITT analysis. Specifically, survival analysis with log rank test will compare time to achieve medical stability by arm while accounting for the correlation within sites; participants who do not meet stability criteria by hospital discharge will be right-censored. In case of any important unbalanced covariate at baseline, Cox proportional hazard ratio model will be used to control for the potential bias due to the confounder. Additionally efficacy outcomes will include the proportion achieving medical stability in each arm, change in %mBMI as compared to baseline, and time to restore HR.

Aim 2. Safety: Primary indicator of safety will be incidence of the following electrolyte abnormalities during hospitalization: 2A) hypophosphatemia (<3 mg/dL), 2B) hypomagnesaemia (≤1.7 mg/dL), 2C) hypokalemia (< 3.5 mEq/L). These AEs will be tracked, recorded, reported to the DSMB for monitoring, and to the IRB and NIH as needed, according to the attached DSMP. Incidence of the electrolyte abnormalities and proportion receiving supplementation to correct electrolyte abnormalities will be compared by arm during hospitalization using Fisher's exact test. Additional safety outcomes: the proportion receiving electrolyte supplementation during the hospitalization between groups will be compared with Fisher's exact test; time to electrolyte nadir will be compared with Wilcoxon rank sum test.

Aim 3. Cost Effectiveness (CE): A decision tree of treatment costs, AEs, health care utilized (including rehospitalizations), and remission will compare the CE between the two study arms. The main CE outcome is incremental cost per additional adolescent remitted. Health care utilization will be costed using national data sources such as acquisition costs for medications, Kids-HCUP for hospitalizations, CPT codes for physician visits and mental health visits, and internet-based costs for lab tests. We will use 2014 US costs and not charges. Indirect costs including missed school and workdays will be assessed and costed using national estimates of wages and salaries of this

age group from the Bureau of Labor Statistics, in order to estimate loss of leisure time (school) or salary time (work).

We will determine the incremental CE ratio (ICER) as:

ICER = $Cost_{LCR}$-$Cost_{HCR}$/Number $Recovered_{LCR}$-Number $Recovered_{HCR}$.

Effectiveness will also be indicated by cost of rehospitalizations avoided (ie, rehospitalizations in LCR-HCR). We will determine the net monetary benefit (NB) of each treatment option as: NB=Effectiveness X Willingness To Pay (WTP) – Cost. A positive difference in NB between treatments indicates CE. We will also calculate an acceptability curve to demonstrate how parameter uncertainty affects the likelihood of selecting the optimal treatment at a given WTP threshold. Cost of treatment will be determined by initial hospitalization and 12 mo follow-up costs (not charges) including AEs and rehospitalizations. The HCUMS follow-up survey will assess indirect costs such as lost school and/or work (wages) using national data sources (**see C.2.c.(2)**).

Effectiveness will be determined per aim 1A; ICER will also use time (incremental cost per additional day of recovery time over 12 mo). Cost efficacy will be assessed with short-term outcomes at end of hospitalization. Per Aim 1B, cost-efficacy will be assessed with other short-term outcomes at the end of treatment (hospitalization period). Cost-efficacy will be defined as hospital cost or charges associated with length of stay; group differences will be compared with Wilcoxon rank sum test.

2.3. Power and Sample-size Considerations

Aim 1. Based on studies of AN remission , **Table 2.A** shows that with N=60 per arm we have 80% power on 2-sided 0.05-level test to detect a 20% difference (8% vs. 28%) if data were cross-sectional (ρ=1). Our longitudinal data will allow detection of smaller effects, especially if the correlation among outcomes is low (ρ <0.8). We anticipate 85% retention and non-differential dropout by arm. Since **time to medical stability** is also expected to differ by at least 12% (**Table 2.B**.), we will be adequately powered for Aim 1B.

Table 2.A Detectable differences in remission---rates:

ρ*	LCR	HCR	Mo---3 Diff
1.0	8%	28%	20%
0.8	14%	34%	20%
0.6	16%	34%	18%
0.4	18%	34%	16%
0.2	20%	34%	14%
0.1	22%	34%	12%

Table 2.B. Detectable differences in time to medical stability-rates

ρ*	LCR	HCR	Difference
1.0	72%	92%	20%
0.8	66%	86%	20%
0.6	66%	84%	18%
0.4	66%	82%	16%
0.2	66%	80%	14%
0.1	66%	78%	12%

*correlation among 5 time points within participant

2.4. Data Management

a. DCC: Dr. Cheng at UCSF will lead the DCC, which will be autonomous and independent of the clinical sites. It is housed in the UCSF Department of Preventive and Restorative Dental Sciences (PRDS). The department is staffed primarily by statisticians and scientific researchers who conduct data-intensive research, collaborative data collection and analyses from multiple sites. They are equipped with an independent network of sophisticated and reliable computer systems with high-level security for protecting health information. The network is maintained by an in-house computer staff, which manages all aspects of the network, including ongoing maintenance, installation and upgrades of hardware, software and structural components such as cabling and servers. Dr. Cheng is the lead biostatistician and routinely guides the work of Master-level statisticians, data managers and programmers. **Dr. Cheng** will continue as faculty biostatistician and DCC leader. She has extensive experience running NIDCR-funded DCCs for clinical trials with more than 8-10 sites nationwide. Thus, UCSF has experience maintaining a distinctly separate but closely coordinated working relationship between clinical sites and data center.

b. Electronic data capture: Both clinical sites are equipped with the same Research Electronic Data Capture (Qualtrics) system for databases, data entry forms, online questionnaires and data validation. Data will be automatically exported to STATA or SAS for analysis using The Data Export Utility. The DCC uses advanced features including branching logic for dynamic data entry form generation, file uploading, data importing, and embedded calculated database fields.

c. Confidentiality: Loss of confidentiality is a recognized risk of participating in clinical research since protected health information, medical history, and demographics are used for the study. Loss of privacy may lead to problems with insurability or social stigmatization. We will make effort to minimize this risk and have systems in place to ensure confidentiality. Data will be de-identified and thereafter handled by ID number, rather than by name. No publications will include the names of patients or identifying information about study participants.

2.5. Retention and Attrition

We expect to retain 85% of our sample through one year of follow-up. This is consistent with other open follow-up studies of AN and feasible given our patients volumes and return rates. We will actively retain participants by providing incentives: movie tickets upon enrollment and a $50 for every follow-up visit attended. Primary analyses will use intent-to-treat longitudinal models that will include outcomes from randomization through the time of dropout or 12 mo, whichever is longer. Secondary analyses will adjust models for baseline covariates that may be associated with loss to follow-up. We anticipate very few missing outcomes because weight and vital sign (medical stability) measures are SOC in AN care during hospital and at follow-up and the majority of patients hospitalized at our programs return to us for follow-up care. Reasons for refusal to participate will be collected from patients and families who decline enrollment.

APPENDIX

MULTI-CENTER RANDOMIZED CONTROLLED TRIAL OF REFEEDING IN ANOREXIA NERVOSA:
The Study of Refeeding to Optimize iNpatient Gains (StRONG)

Appendix Table 1. Amendments to the Protocol

Protocol version	Section changed	Amendment description & reason	IRB approval and/or other documentation date
1.1	3.1 Treatment and Follow-up	Oral nutrition supplement to replace refused food contains 1.5 kcal/mL; previously listed as 1.06 kcal/mL, to reflect actual clinical practice	IRB approved 12/01/2015
	3.1 Treatment and Follow-up	Electrolyte replacement protocol developed for more severe levels of low serum electrolytes	
	3.1 Treatment and follow-up	Nutrition intake is assessed via 24-hour recalls at each follow-up time point to reduce participant burden	
	2.1 Study Population	Added one exclusion criterion: extremely malnourished patients, admitted with mBMI <60%, will no longer be eligible to enroll in the study, as they are at higher risk of medical decompensation.	Posted on clinicaltrials.gov 05/12/2016
	3.1 Treatment and follow-up	Follow-up visits will be defined as time since discharge instead of time since admission. This will ensure that time elapsed will be comparable among participants despite differing lengths of admission.	
1.2	3.2 Data Collection	Self-reported EDE-Q (5-10 minutes) will replace the lengthy interview-based EDE (60-90 minutes), based on recent evidence that it serves as a valid proxy for measuring severity of eating disorder psychopathology, with significant reduction in participant burden and personnel cost.	IRB approved 01/05/2016 NIH in progress report 05/08/16 Posted on Clinicaltrials.gov 05/12/2016
	2.1 Study Population	Eligibility criteria updated to reflect actual clinical practice: to be eligible for participation, orthostatic increase HR from lying to standing of 35 bpm	IRB approved 05/03/2016
1.3	3.1 Treatment and follow-up	Discharge criteria based on SBP only, not DBP	IRB approved 05/19/2017

Appendix Table 2. Amendments to the Statistical Analysis Plan*
*** All amendments were made and documented prior to locking of database for analysis**

Section changed	Amendment description & rationale	Amendment date & documentation
2.2 Outcomes	**Amendment 1: End-point for AIM 1B shortened to in hospital treatment period** **Rationale:** To match the timeframe for the safety outcome and to better capture the efficacy of this relatively short intervention (less than 2 weeks in hospital) within a long, open follow-up trial. Further, to allow timely dissemination of findings. [Citation: IOM guideline, *Sharing Clinical Trial Data: Maximizing Benefits, Minimizing Risk,* pg 118: Investigators "may publish the primary trial endpoints despite ongoing longer-term participant follow-up; in this case, the last participant's last visit may not occur for some time, and hence the full analyzable data set may not be complete at the time of the original publication."] Timeframe for AIM 1B specified as 2 weeks and posted on clinicaltrials.gov Project officer, Dr. Karen Winer approved analysis of short-term (in-hospital) outcomes by arm (DSMB notified 7/03/19, randomization code was broken) Short-term database locked	 06/30/2015 05/26/2019 07/31/2019
2.2 Outcomes	**Amendment 2: Analytic approach for AIM 1B changed from mixed effects regression modeling to survival analysis** **Rationale:** survival analysis chosen to examine time to restore medical stability in hospital (amended AIM 1B), rather than mixed effects regression modeling to examine medical stability over 12-month follow-up. This is a more appropriate approach to assess "time to" outcome, which accounts for the variable lengths of hospital stay and allows participants who were discharged before medical stability was restored to be right-censored. Change in "time to" analysis documented in NIH Progress Report Data Coordination Center documented decision to use survival analyses for AIM 1B	 05/05/2017 10/17/2017
2.2 Outcomes	**Amendment 3: Analytic approach for AIM 2 (safety) changed from Cox regression modeling to basic non-parametric testing** **Rationale:** Originally planned approach (Cox regression models) assumed high incidence electrolyte abnormalities based on prior studies reporting rates up to 48%. However, ongoing AE monitoring during the trial revealed very low incidence and therefore basic parametric methods were chosen to allow clinical interpretation of the results. DSMB reports since 2017 (signed by DSMB members and sent to POs, Dr. Graves and Dr. Winer)	 02/17/2017 02/20/2018 02/15/2019

RESEARCH STRATEGY

I. SPECIFIC AIMS

Anorexia nervosa (AN) is an illness commonly diagnosed in adolescence with low recovery rates and high healthcare costs. The major medical complication of AN is malnutrition. Caloric restriction, purging and other weight control behaviors can lead to medical instability (abnormal vital signs) requiring hospitalization. The primary goal of hospitalization is to restore medical stability by reintroducing nutrition, or "refeeding" [1, 2]. Within 12 mo of discharge, 43% [3] of patients will require medical rehospitalization. This contributes to a costly course of recovery, given that eating disorders are the most expensive primary mental health diagnoses requiring hospitalization [4]. Several lines of inquiry seeking to identify characteristics or short-term outcomes that may predict better recovery from AN point to rapid short-term weight gain as a strong predictor of long-term outcomes. Greater weight gain in hospital predicts weight recovery at 12 mo [5-7] and greater weight gain during the first 3-4 wk of psychotherapy (1.7-1.9 lb/wk) predicts full remission at 12 mo [8]. Unfortunately, the currently recommended approach, Lower Calorie Refeeding (LCR), is associated with slow weight gain and prolonged hospital stay. Treatment is now moving sporadically toward Higher Calorie Refeeding (HCR) in the hope of improved recovery but with insufficient evidence to guide best practices.

Refeeding has been approached with extreme caution since the refeeding syndrome, characterized by rapid electrolyte shifts, delirium and cardiac arrest in response to the influx of nutrients was first described around WWII [9, 10]. Following documentation of this syndrome in patients with AN [11-15], conservative, consensus-based recommendations for LCR were developed [16-18]. LCR typically begins around 1200 kilocalories (kcal) per day and advances by 200 kcal every other day [16-18]. Our preliminary studies demonstrating that the long-standing clinical observation of initial weight *loss* and long hospital stay was associated with lower starting calorie levels [19] have contributed to recognition of the "underfeeding syndrome" [15]. In subsequent studies, we reported that HCR produced faster weight gain and shorter hospitalization [20, 21]. While no increased risk of refeeding syndrome has been reported using HCR, the variety of electrolyte supplementation protocols being used to manage risk have not been examined [22].

Findings from these observational and retrospective studies are being rapidly accepted by many clinicians and insurers, and some programs are integrating HCR into practice. <u>However, there are major gaps in the evidence necessary to adopt HCR as the new standard of care</u>: 1.) It is not known if HCR impacts clinical remission, which is typically defined as the combination of weight *and* cognitive recovery at 12 mo. 2.) The safety of HCR has not been confirmed. While examination of the full spectrum of the refeeding syndrome (including the rare occurrence of death) would require a large trial, the hallmark electrolyte imbalances occur frequently and still have not been systematically examined on differing refeeding protocols. 3.) The shorter hospital stay associated with HCR is of great interest to clinicians, families and insurers hoping to contain healthcare costs, however the true cost-effectiveness (cost in relation to recovery) must be explored.

We propose to conduct a randomized controlled trial (RCT) at two sites to directly compare HCR and LCR for refeeding in AN. To accomplish the following aims, 120 adolescents will be enrolled upon admission to hospital for malnutrition secondary to AN and randomized 1:1 to HCR (beginning with 2000 kcal and advanced 200 kcal/d) or LCR (beginning at 1400 kcal/d and advanced 200 kcal every other day) until medical stability is restored. Participants will be followed for 12 mo after randomization: Daily while in hospital and at follow-up 10 dy,1 mo, 3 mo, 6 mo, and 12 mo after randomization. <u>These findings will contribute to the development of evidenced-based refeeding approaches in AN.</u>

Our study has three main aims. We will compare:

1: Efficacy of LCR vs. HCR over 12-mo follow-up. We hypothesize that LCR and HCR will differ by *achievement and maintenance of*: (1A) clinical remission during 12 mo follow-up, defined by achievement of both (i) weight ≥ 95% median BMI (MBMI) for age and sex, and (ii) Eating Disorder Examination (EDE) global score within 1 SD of clinical norm [20], and (1B) medical stability during 12 mo follow-up defined by published vital sign thresholds [23].

2: Safety of LCR vs. HCR during initial hospitalization. We hypothesize that LCR and HCR will *not* differ by *incidence of*: 2A) hypophosphatemia (≤3 mg/dL), 2B) hypomagnesaemia (≤1.7 mg/dL), and 2C) hypokalemia (≤3.5 mEq/L).

3: Cost-effectiveness (CE) of LCR vs. HCR. We hypothesize that HCR will be more cost-effective than LCR, as determined by cost (including costs of initial and re-hospitalizations, 12 mo follow-up, other care, and safety/adverse events (AEs) and effectiveness per adolescent recovered (defined in AIM 1A and B).

II. SIGNIFICANCE

II.A. Overview: AN is the most deadly psychiatric illness, in part because it results in malnutrition and acute medical sequelae. The mortality rate has been estimated as high as 5.0% [24] and rates of clinical remission are low, ranging from 18-55% [24]. Diagnoses of AN are expected to increase [25] with the fifth edition of the Diagnostic and Statistical Manual (DSM-5). The criteria for diagnosing AN are now more inclusive: amenorrhea and weight below 85% of expected are no longer required, while a new diagnosis of atypical AN will include the growing number of formerly overweight patients who present with malnutrition due to weight loss. In addition to more boys being diagnosed [25], the population who meet criteria for atypical AN is more racially/ethnically diverse and has increased an estimated 5-fold in the past 6 years [26]. The growing prevalence and changing face of AN underscore the need to develop effective treatments.

Malnutrition due to caloric restriction, excessive exercise and other dieting behaviors, can quickly result in medical instability, even in young people who were recently healthy and well nourished. The abnormal vital signs defining medical instability were recently updated [27] as follows: bradycardia (daytime heart rate (HR) < 50 bpm or night time HR < 45 bpm), hypotension (BP <90/45 mmHg), hypothermia (< 36° C) and orthostasis (increase in HR > 20 bpm or decrease in systolic BP > 20 mmHg or decrease in diastolic BP > 10 mmHg from lying to standing). In such cases, hospital admission, bed rest and a prescribed diet for refeeding are recommended. Medical stability is typically restored within a few weeks [1] and patients leave hospital with a long road to recovery ahead; 43% will require additional hospitalization in the first year [3]. Return of menses may take more than nine months after hospital discharge and typically occurs at a weight corresponding to 95% MBMI [28, 29]. However, eating disorder cognitions (such as distorted body image) can remain powerful at "normal" weight; therefore clinical remission is defined as weight and cognitive recovery together [30].

Greater weight gain in hospital and during early treatment (the first 4 weeks) predicts of weight recovery [5-7] and clinical remission [8] at 12 mo. Unfortunately, slow weight gain and prolonged hospital stay became part of the expected course for AN [31] in the decades since LCR has been the standard of care in AN. The American Psychiatric Association [16, 17], the Academy of Nutrition and Dietetics [18] and others [32] recommend starting around 1200 kcal per day and advancing slowly by about 200 kcal every other day. The resulting slow weight gain was formerly attributed to fluid shifts [33, 34] and changes in metabolic rate [35]. Our 2012 study at the University of California San Francisco (UCSF) was the first to demonstrate that it was associated with lower starting calorie levels [19]. These findings contributed to the recent recognition of the "underfeeding syndrome", characterized by prolonged illness and even death due to overly cautious refeeding [15].

The original intent of the "start low and go slow" LCR approach was to minimize risk for the refeeding syndrome. The clinical features of this syndrome include cardiac arrhythmias, cardiac failure or arrest, muscle weakness, hemolytic anemia, delirium, seizures, coma, and sudden death [36]. Risk is highest in the first seven days [2] when refeeding is initiated in a starved individual. The insulin surge in response to the influx of nutrients (particularly carbohydrate) causes a massive shift in electrolytes and fluids from the extra- to the intracellular space as the cells take up glucose. The hallmark feature is hypophosphatemia (≤3 mg/dL[2]), however hypomagnesaemia (≤1.7 mg/dL) and hypokalemia (potassium ≤3.5 mEq/L) may also occur [21]. Since it was first described around WWII [9, 10], the refeeding syndrome was documented in patients with AN [11-15] and LCR has been used broadly to ensure safety.

Our subsequent studies at UCSF and Stanford University suggest that HCR is feasible to improve outcomes in hospital (**see Table 1**). At UCSF, our prospective observational study of 56 adolescents hospitalized with AN followed daily in the Pediatric Clinical Research Center found nearly double the rate of weight gain and almost six days shorter hospitalization in a group starting at 1775 kcal/d on average as compared to those starting around 1165 kcal/d [20]. At Stanford, our large retrospective study of 310 adolescents compared two groups starting at an average of 1550 vs. 1165 kcal/d and found more than 3 days shorter hospital stay [21]. These preliminary findings are being rapidly translated into practice. However, without sufficient evidence to guide best practices, a wide variety of HCR approaches are being implemented. For example, differing rates of caloric advancement might explain why we found faster rates of weight gain in our UCSF study but not Stanford. There is also wide variation method of delivery of HCR: meal-based approaches are preferred in the U.S [20, 21], whereas enteral (tube) feeding is reported in Europe [37-39] and Australia [40]. Our programs use meal-based HCR, where food is served on bedside trays, formula is given orally only as needed to replace refused foods, and enteral feeding is reserved as a last resort.

As clinical practice moves toward with HCR in various forms, the questions of safety and long-term outcomes are paramount. A large, nationwide trial would be required to examine the full range of clinical features associated with the refeeding syndrome: only a handful of cases of cardiac arrest and death have been reported in the AN literature [12, 41, 42]. Research to date has focused on the associated electrolyte disturbances and the proposed study will build on this. It is difficult to interpret the available data on electrolyte abnormalities during HCR [20, 21, 43, 44] because a wide variety of approaches are being used to treat them [22]. Some programs initiate prophylactic phosphate supplementation when HCR commences, whereas another program reported that only 1 of 30 patients required electrolyte replacement for low phosphorus [44]. Our programs at UCSF and Stanford are using electrolyte replacement to treat low and/or declining serum phosphorus [22]. Using this method, the Stanford study observed an overall rate of 15.8% hypophosphatemia, with no differences in rates of hypophosphatemia, hypomagnesemia or hypokalemia between HCR and LCR groups. At UCSF, we also reported no differences in electrolyte abnormalities with 36% of participants receiving electrolyte replacement [20]. This overall rate similar is similar to other programs [43], but it appeared as though more HCR participants received electrolyte replacement than LCR (43 vs. 28%), suggesting systematic bias [20]. Thus, we cannot determine whether there are differences in electrolyte abnormalities based on caloric level. The proposed study will answer this questions using a standardized electrolyte monitoring and replacement protocol (**see B.4.c.**), which will be identical between study groups and sites.

The long-term impact of HCR is unknown and this prevents weighing the possible benefits against any potential risks. In preliminary data from our current project (1R03HD077421-01), weight recovery at 12 mo appears slightly better in HCR than LCR **(see IV.A.2.b).** However, the retrospective chart review data and small sample size prevent us from determining whether this apparent difference is clinically significant and how much is attributable to differing body weights at baseline. Selection bias is also possible, as HCR may have been prescribed to heavier patients. The proposed study will address these caveats with a randomized, prospective design. A second unanswered question arises from studies reporting increased anxiety and stress in proportion to calorie load in AN patients [45-48]. These findings have prompted some clinicians to ask whether HCR could actually *impede* cognitive recovery. Will examine this potential unintended consequence as part of our primary aim; such a finding would lay groundwork to explore mechanisms (such as meal-time stress) in future studies. Finally, rehospitalization rates warrant further examination. In our preliminary data the LCR group appears to spend more time rehospitalized, which is consistent with findings from the only RCT of refeeding in AN to date. Rigaud et al. compared higher calorie tube feeding (N=41) to lower calorie meal-based refeeding (N=40) and found sooner rehospitalization in the meal group with no differences in weight at 12 mo [38]. The nasogastric method of delivery, adult study population and long hospitalization (2 mo) prevent direct comparison, but this study provides support for our hypothesis that LCR will result greater rates of relapse.

AEs and/or medical instability requiring rehospitalization for additional rounds of refeeding contribute to the high healthcare costs of AN. Indeed, eating disorders are the most expensive diagnosis among the recognized "common and costly" primary mental health diagnoses in pediatrics [4], with an average charge of $46,130 per hospitalization. Of course, the true "cost" of AN reaches far beyond the hospital bill into the life of the affected adolescent. The full episode of care includes both the direct cost of initial hospital stay and rehospitalizations (including emergency room visits) as well as the indirect costs such as days missed at school and work. The proposed study will compare the cost per adolescent recovered on HCR and LCR using a decision tree of treatment costs including AEs, rehospitalizations, and recovery outcomes. This comprehensive examination of CE is novel in the field of AN and much needed to weigh difficult treatment decisions.

II.B. Conclusions: Balancing the potential risks of the refeeding syndrome with the need to maximize weight gain during refeeding in hospitalized patients with AN represents a fundamental paradox for clinical practice. While the conservative recommendations for lower calorie diets minimize refeeding risk, they also contribute to the underfeeding syndrome. Our preliminary studies indicate that HCR is feasible and beneficial in hospital, however no studies have directly compared the long-term efficacy and safety of the two approaches. This RCT is the next essential next step to building evidence-based approaches to refeeding.

III. INNOVATION

The field of AN is poised to make major shift in clinical practice in light of recent evidence that LCR, the cautious approach to refeeding used since WWII, may actually thwart recovery. Clinicians are eager to implement better approaches but there is little evidence to guide clinical practice. Thus, the timing of this proposal is ideal for rapid translation. First, this would be the first RCT to compare HCR and LCR in adolescents with AN. We are proposing to utilize two study sites to maximize sample size in this relatively rare

illness and answer the research questions in a timely manner. Second, our geographic location, diverse patient populations and inclusion of the new DSM-5 diagnosis of atypical AN will result in a study sample that is more diverse in race/ethnicity and sex (boys). Studies of AN traditionally been limited in diversity because the presenting population is mostly White girls [49]. Third, the investigators at both sites have contributed heavily to the science leading up to this proposal and we have established clinical research protocols that can be reliably disseminated at both sites. The fourth innovative aspect of the proposed study is the interdisciplinary nature: we plan to explore the relationship between nutritional rehabilitation and medical and psychological recovery, areas that are too often studied separately. Finally, the proposed examination of CE is novel in the field of AN and will generate crucial information for clinicians, adolescents and their families, making care decisions in the wake of a "common and costly" diagnosis with known poor recovery.

IV. APPROACH

A. Preliminary Studies

A.1. Evidence for the underfeeding syndrome

a. The "stabilization" phase: Solanto & Golden (1994) were first to publish daily weight gain trajectories in AN participants showing initial weight loss on LCR [31]. The purpose of this study was to assess rate of weight gain under two behavioral contracts differing in the amount of weight gain required (0.8 lb vs. 1.2 lb in 4 days) to increase privileges (e.g. telephone). Refeeding was initiated on LCR at 1000-1200 kcals/d. In the 53 female adolescents aged 9-23 years with AN who met inclusion criteria, rate of weight gain increased in the HC group (contract 2) but in both groups there was a 5-7 day "stabilization phase" during which weight initially dropped. This study was important as it provided the first documentation of the long-standing clinical observation of initial weight *loss* in hospitalized AN patients.

b. The association between initial weight loss, long hospital stay and LCR [19]: SHAAN was an observational study with data collected prospectively throughout the course of hospitalization. This project began at UCSF in 2002 funded by the CTSI (UL1 RR024131, PI Garber, Co-I Moscicki). Adolescents with diagnosed AN ages 9-20 years and no previous hospital admissions for AN were enrolled upon hospital admission for medical stabilization. Participants were moderately malnourished with a mean BMI of 16.1(0.3) kg/m^2, bradycardic and hypothermic [50]. Thirty-five participants enrolled 2002-2009 and refed starting between 800-2200 kcal/d with a mean (SEM) of 1205(289) kcal (consistent with LCR). Calorie prescriptions increased to 2668(387) over 17 days. No participants had clinical symptoms of the refeeding syndrome; 20% had low serum phosphorus (≤3.0 mg/dL). %MBMI increased from 80.1(11.5) to 84.5(9.6); overall gain was 2.10(1.98) Kg. Paired t-tests compared daily change in %MBMI.

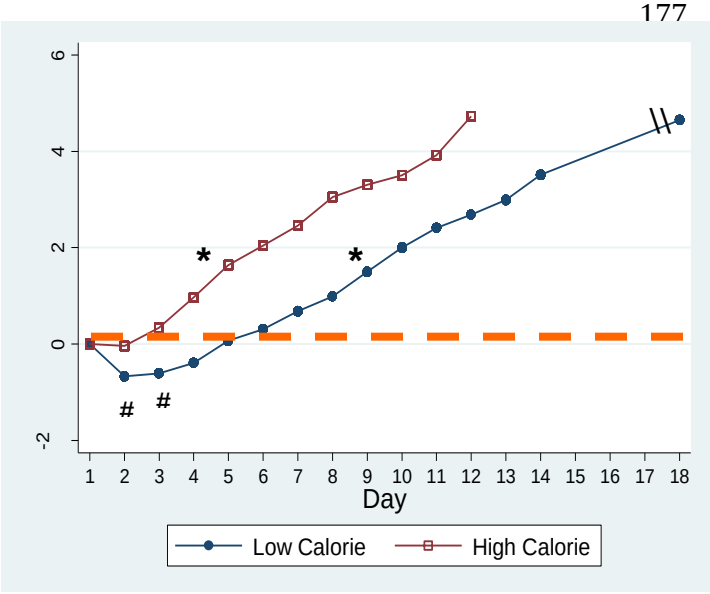

Figure 1: Change in %MBMI on LCR vs. HCR
--- baseline %MBMI calculated from Day 1 height and weight
 # Day 2 and Day 3 significantly lower than Day 1 (p <0.05).
*** significantly greater than Day 1 (all p <0.05)**

We found an association between initial weight loss and lower kcal upon admission [20]. Weight loss of 0.60 (0.57) Kg occurred in the first 3 days; no gain was observed until day 8. In multivariate linear regression models adjusted for %MBMI and HR upon admission (to control for degree of malnutrition), higher kcal was associated with faster weight gain (β = 0.0002; 95% CI 0.0001, 0 .0005; p=0.016) and shorter hospital stay (β = -0.0092; 95% CI -0.0152, -0.0008; p=0.013). For every 100-calorie increase in prescription at baseline, rate of %MBMI gain increased 0.02% per day and stay days decrease 0.9 days. This is called the "underfeeding study" because it demonstrated the association between LCR, poor weight gain and long stay in hospitalized adolescents with AN.

A.2. Evidence for Higher Calorie Meal-Based Refeeding

a. Time to achieve weight gain and medical stabilization HCR: Our programs and others began increasing calorie prescriptions in response to the studies above and other reports of higher calorie approaches to refeeding in AN [40, 43]. This shift in clinical practice created an experimental opportunity to compare the two

approaches. We enrolled new participants in SHAAN from 2009-12 refed on HCR (N=28) and utilized our former study participants on LCR (N=28) as historical controls. HCR began at mean (SEM) of 1764(60) kcal, LCR began at 1093(28) kcal (p<0.001). Unpaired t-tests between groups showed no differences in %MBMI, age, HR, temperature or hydration upon admission. HCR advanced more quickly (p=0.024) and were 250 kcal greater upon discharge (p=0.015). There were no differences in serum phosphorus, however more HCR participants were supplemented (12/28 (43%) vs. 8/28 (29%), p=0.273). Weight gain trajectories are shown in **Fig 1**. No average weight loss was observed in HCR. Rate of weight gain was double in HCR: 0.46(0.04) vs. 0.26(0.03) %MBMI per day in the, or 0.27(0.03) vs. 0.14(0.02) kg per day (p<0.001). Average hospital stay was 5.7 days shorter (p<0.001) in HCR; therefore there was no difference in %MBMI at discharge (p=0.173). We found shorter hospital stay, faster weight gain with no increased evidence of risk of the refeeding syndrome (using phosphate supplementation) on HCR compared to LCR. However, this study is limited as an observational study of clinical practice: the sample size was relatively small, feeding groups were not rigorously defined and supplementation was varied.

b. Safety of HCR in large retrospective study: Safety was, and remains, the major consideration in HCR. At Stanford we retrospectively reviewed the electronic medical records in all participants 10-21 years old with AN who were hospitalized for the first time in our program between Jan 2007 to Dec 2011 to compare weight gain, length of stay and prevalence of hypophosphatemia, hypomagnesemia, and hypokalemia of LCR and HCR [21]. Hypophosphatemia was defined as ≤3.0 mg/dL, hypomagnesemia as ≤1.7 mg/dL, and hypokalemia ≤ 3.5 mEq/L. LCR included all participants starting on <1,400 kcal/d and HCR started ≥1,400 kcal/d, with 95% of subjects in the HC group starting on 1400-2000 kcal/d.

The characteristics of these 310 participants are shown in **Table 1**. Mean starting kcal in LCR vs. HCR were 1,163(107) and 1,557(265) kcal/d. With these calorie groups, we did not find initial weight loss or differences in rate of weight gain, however days in hospital was significantly reduced in HCR [13.0(7.3) vs. 16.6(9.0) d; p < .0001]. Regarding safety, we found no differences in rates of hypophosphatemia (p=0.49), hypomagnesemia (p=1.0) or hypokalemia (p=0.35) between groups. Hypophosphatemia was associated with %MBMI on admission (p=0.004), consistent with our previous studies, but not caloric intake (p=0.14). Importantly, results were similar when we restricted the analysis to N=49 severely malnourished participants (MBMI < 70%). These findings provide further support for HCR and suggest that it is feasible even for those with severe malnutrition.

c. Long-term follow-up of SHAAN participants refed on LCR vs. HCR: There are currently no published long-term data on meal-based refeeding. Our current project (1R03HD077421-01, PI Garber, Co-I Moscicki, co-I and lead biostatistician Hilton) is examining outcomes for one-year after hospital discharge in our SHAAN participants. Our hypothesis is that HCR would lead to earlier hospital discharge without negative effects; specifically no greater rate of rehospitalization. We are submitting the results for publication. Weight gain trajectories for study groups defined by Day 1 calories (1000, 1200, 1400 and 2000) are shown in **Fig 2**. These retrospective data show no differences in weight recovery between groups, with more total days in hospital for LCR participants. Including initial stay and rehospitalizations for AN, LCR participants (starting at 1000 or 1200 calories) spent more than 9 additional days in hospital over 12 mo follow-up (p=0.035). The implication of this finding, that the high cost of additional hospital time confers no advantage in long-term weight recovery, will be tested in the proposed study.

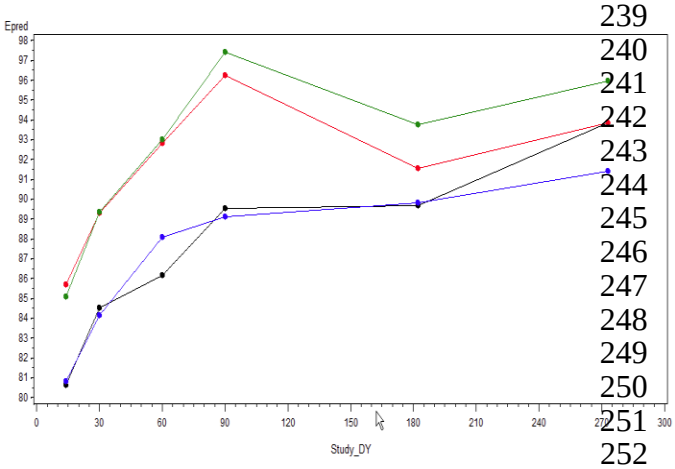

Figure 2: Change in %MBMI by start calorie prescription quartile (1000 black, 1200 blue, 1400 red, green 2000)

A.3. Summary of preliminary findings: These studies strongly support the notion that LCR contributes to underfeeding, whereas HCR safely speeds weight gain and shortens hospital stay in moderately malnourished patients with AN. However, these data are observational and subject to clinical bias: diets were implemented and electrolytes were prescribed based on clinical judgment. The proposed study, with randomization to defined HCR and LCR with protocolized electrolyte monitoring and replacement, will contribute to evidenced-based recommendations for refeeding in AN.

B. Proposed Study

Current recommendations to guide the clinical care of AN patients hospitalized with medical instability due to

malnutrition are based solely on retrospective or observational studies and/or clinical experience. No studies to date have prospectively tested HCR and the long-term impact on recovery is unknown. Consensus has developed over recent decades that patient safety can only be guaranteed using LCR. The entrenchment of clinical practice without supporting evidence is a widely recognized dilemma in healthcare [51]. While RCTs are considered the "gold standard" to establish evidence-based medicine, until recently there was insufficient data to propose such a study of refeeding in AN. We now have preliminary findings to indicate that LCR might be too cautious and that HCR appears feasible and may improve long-term recovery. Thus, we are poised to compare these two treatments in a parallel, randomized fashion.

B.1. Study Design: The purpose of this multi-center randomized controlled trial is to compare LCR vs. HCR refeeding strategies for hospitalized adolescents with AN. Participants will be recruited upon hospital admission at two centers (UCSF and Stanford) to maximize sample size, and randomly assigned 1:1 within site to one of the two strategies. A total of 120 participants age 12-24 yrs who meet DSM-5 diagnostic criteria for AN and atypical AN (**see IV.B.2.**), and present as medically unstable due to malnutrition will be enrolled. Treatments will not be blinded, since both the patients and clinicians who work with this population are highly skilled at estimating kcal and would be able to determine their group assignment by simply viewing the meal trays. In addition, target kcal will be reached faster in HCR and this would be apparent on physician orders. An important exception is the research assistant collecting the EDE, who will be blinded so as not to bias the interview. The proposed study is powered to detect a meaningful difference in clinical remission (Aim 1).

B.2. Study population: We will expand inclusion criteria from previous studies to capture a broader representation of patients by including diagnoses of AN and atypical AN as per the new DSM-5 and including participants with multiple admissions.

a. Inclusion/Exclusion: Adolescents hospitalized for medical instability secondary to malnutrition will be eligible as follows. Inclusion criteria: diagnosis of AN, atypical AN [52], age 12-24 years, no hospital admissions for the previous six months, and meet hospitalization criteria (daytime HR < 50 bpm or night time HR < 45 bpm, BP <90/45 mmHg, temperature < 36° C or orthostasis defined by increase in HR > 20 bpm or decrease in systolic BP > 20 mmHg or decrease in diastolic BP > 10 mmHg from lying to standing) [27]. Exclusion criteria: diagnosis of bulimia nervosa [DSM-5], currently in remission (as defined by weight and EDE score per Aim 1), admission for food refusal without malnutrition, current pregnancy, chronic disease (e.g. immune/endocrine disorders, pulmonary, cardiac, or renal disease), current suicidality or psychosis.

Both of our programs draw patients from the Bay Area, a highly diverse region including several major metropolitan areas (e.g. San Francisco, Santa Rosa, San Jose, Fresno and Sacramento). At UCSF, 31% of our patients self-describe as "non-White", within this group is 47% non-White Hispanic, 5% Black, 24% Asian and 24% Other, and 37% of these patients have public insurance. At Stanford, the clinic population is 18% non-White. By comparison, 87.6% of the patient population with AN is White across a national sample of 14 programs [53].

Table 1: Comparison of historical AN study populations by site and refeeding strategy

	Demographic and clinical features	Stanford (N=310) [21] LCR (N=88)	Stanford (N=310) [21] HCR (N=222)	Stanford (N=310) [21] P-val ^	UCSF (N=56) [19] LCR (N=28)	UCSF (N=56) [19] HCR (N=28)	UCSF (N=56) [19] P-val ^
Baseline							
1	Age, yr	16.2 (2.4)	16.1 (2.3)	.69	16.2 (2.1)	16.1 (2.4)	.88
2	Admit BMI, kg/m2	15.9 (2.2)	16.1 (1.7)	.48	15.8 (2.5)	16.6 (2.1)	.19
3	Admit %MBMI	77.9 (9.6)	78.7 (7.8)	.44	77.6 (12.1)	81.9 (9.5)	.15
4	Initial prescribed kcal	1,163 (107)	1,557 (265)	<.001	1,093 (149)	1,764 (318)	.000
Follow-up							
5	Length of stay, days	16.6 (9.0)	13.0 (7.3)	.000	17.6 (6.52)	11.9 (5.41)	.000
6	Discharge %MBMI	84.3 (8.2)	83.7 (6.9)	.54	82.3 (9.7)	85.7(8.6)	.17
7	Rate of chg %MBMI (wk1)	0.57 (.30)	0.55 (.37)	.50	0.26 (.17)	0.46 (.22)	<.001
8	Weight gain, kg	3.6 (2.3)	2.9 (1.9)	.01	2.49 (2.0)	2.74 (1.5)	.60
9	Discharge kcal	2,531 (608)	2,560 (598)	.70	2,642 (404)	2,893 (338)	.02

Values are means (SD); ^ P-value from unpaired t-test between LCR and HCR groups

Our programs treat highly diverse patients with minimal inter-site variability in ranges of diagnoses and disease severity. **Table 1** lines 1-3 show that participants in previous studies at our sites were nearly identical in key characteristics including age and %MBMI (an indication of degree of malnutrition). Our sites have a long

history of working together, share referrals on a regular basis and cross-train faculty and trainees (four faculty in Eating Disorders Program at Stanford completed fellowship training at UCSF). Thus, we have very similar clinical approaches to HCR and LCR. This is evidenced by similarities in some of our outcomes, such as shorter length of stay with HCR (**Table 1 line 5**). However, our rates of weight gain are different. Finally, we both show similar discharge %MBMI on LCR and HCR and therefore it is unclear whether the HCR group leaves hospital at any advantage. Thus, while there is enthusiasm for adopting HCR into practice, equipoise exists with respect to both the short-term outcomes in **Table 1** and the potential long-term outcomes.

b. Participant recruitment and consent: Participants and their parents will be approached upon hospitalization to sign assent (for those < 18 yr) and consent, respectively, within 24 hr of hospitalization. This may occur in the clinic when they are deemed medically unstable and waiting transfer to the hospital or in the hospital if admitted directly. Consent will include permission to collect study data in addition to review medical records and itemized hospital bills as needed.]. If a participant turns 18 yr while enrolled, s/he will be reconsented. This proposed study is under review for approval by the UCSF and Stanford Human Subjects Protection Committees. Approval for our SHAAN study has been renewed and updated continually at UCSF since 2002.

B.3. Randomization: Participants will be stratified by site and randomly assigned 1:1 to the two intervention strategies within 24 hr of hospital admission. The Data Coordination Center (DCC) **(see C.6.)** at UCSF will provide a secure unpredictable allocation sequence (e.g. A B B A …) of envelopes to each site, labeled with sequential study ID numbers. The sequences will be generated using random block sizes to maximize balance between arms throughout accrual while ensuring the sequences remain unpredictable. As patients consent to study participation, clinical-research staff will assign the next available study ID number in sequence, identify the allocated intervention arm, and inform participants and their families of the assignment. In turn, the clinical-research staff will provide the linked study ID number and Medical Record Number to the DCC, which will store this Personal Health Information in a HIPAA-compliant manner along with the intervention assignment. At the end of accrual, the clinical-research staff will return envelopes for unassigned study IDs unopened to the DCC.

B.4. Study Interventions

a. Study groups: Upon randomization, the LCR group will begin with 1400 cal per day; HCR group will commence at 2000 kcal. Given our previous findings, recognition of the so-called underfeeding syndrome and recent clinical experience, we will not test a 1200 calorie diet even though it is still currently recommended [16-18]. Our previous studies have adequately demonstrated that a 1200 kcal diet produces initial weight loss [20, 31] and therefore do not feel it is ethical to assign participants to this treatment. We chose 1400 kcal to start because in our previously study of LCR, weight loss ceased on day 3 in hospital when diets averaging 1411(299) kcal were prescribed. Diet prescriptions will increase by 200 kcal every other day in LCR and 200 kcal per day in HCR until a target level is reached. **Target kcal** are calculated upon admission as percent of energy needs using Estimated Energy Requirement (EER) equations from the Institute of Medicine [54]. These equations are used clinically to set goals for caloric advancement although they are known to underestimate energy needs in patients with anorexia [55]. Therefore, we maximize these estimations by using **target weight** corresponding to the MBMI for age and sex (rather than current weight), a moderate activity factor of 1.2-1.3 (despite bed rest), and additional 500 kcal (if current weight < the MBMI).

b. Intervention (refeeding protocols): During hospitalization, participants will follow a meal-based refeeding protocol that calls for eating three meals and three snacks per day, served on trays at the bedside, in the presence of 'Room Sitters'. The calorie level of the diet will be prescribed by the physicians per study protocol and the meals will be prepared by hospital foodservice. The study PI (Garber) will work with the Research Registered Dietitian (RD) and nutrition staff at both sites to ensure that menu selections fit the general macronutrient distribution of 30-40% fat, 15-25% protein and 35-55% carbohydrate. Menus will be continually analyzed (Software v.17.9.5, Computrition, Inc., Chatsworth, CA) to ensure conformance to this distribution as menu items are added or change over time. Dietetic Technicians will keep daily calorie counts, per Standard of Care (SOC), showing actual kcal consumed from food and formula.

A high energy liquid supplement ("formula") providing 1.06 kcal per mL (250 kcal per 240 mL can) will be used orally as needed to replace kcal refused in meals or snacks per a standard calorie replacement protocol. We previously reported a greater than 98% concordance between kcal prescribed and actual kcal ingested using this method, as well as an equal proportion of kcal intake from formula in LCR and HCR groups [20]. This finding supports our clinical observation that HCR meals can be completed without additional reliance on drinking formula. However, most AN patients do experience discomfort during refeeding and therefore all participants will receive SOC meal support including emotional support and techniques such as distraction. All

beverages will be weighed and measured before placement on the tray, with a 1 L per day free water restriction. Room sitters will observe intake of all meals/snacks and remain in the room for 45 min afterwards.

c. Monitoring of electrolytes and correction of abnormalities: Blood for electrolytes will be obtained between 5 and 7 am every 24hr for the first 7 days and more frequently if needed. Since the risk of refeeding decreases after the first week, day 8 electrolytes will be monitored every other day starting on day 8 unless there is continued evidence of abnormalities. Electrolyte abnormalities (serum phosphorus ≤3 mg/dL, magnesium ≤1.7 mg/dL, or potassium ≤3.5 mEq/L) will be corrected with a standardized protocol for both sites [2, 56]. Patients with hypophosphatemia will be treated with sodium potassium phosphate, 250 mg per packet (8 mmol phosphorus, 7.1 mEq potassium), one packet three times a day by mouth for a serum phosphorus between 2.5 and 2.9 mg/dL, and two packets (500 mg) three times a day for a serum phosphorus < 2.5 mg/dL. Those with hypomagnesemia will be prescribed magnesium amino acids chelate (133 mg elemental Mg per tablet), one tablet three times a day by mouth. Declining phosphorus levels that are in the normal range will not be treated. Participants will also receive a SOC supplement regimen including 500mg elemental calcium twice per day and an adult multivitamin with minerals once per day.

b. Study time points: Participants will be followed prospectively in hospital with daily measures of calorie and supplement intake and weight from admission through discharge. Patients will be discharged when medically stable, with the primary criterion of heart rate > 45 bpm for least 24 hr. Upon discharge, the project coordinator will schedule participants for five follow-ups (**see Table 2**) as time points established by our preliminary studies. Day 10 is the time nearest hospital discharge for both groups where medical and electrolyte stability is expected. Month 1, 3, 6 and 12 all contributed meaningfully to the weight recovery trajectory in our preliminary follow-up study (mo 9 was collapsed because it was not different than mo 6 or 12). Finally, these time points are sufficiently coordinated with SOC follow-up so as to minimize participant burden and maximize retention.

B.5. Retention and Attrition: We expect to retain 85% of our sample through one year of follow-up. This is consistent with other open follow-up studies of AN [57] and feasible given our patients volumes and return rates (**B.2.a.**). We will actively retain participants by providing incentives: movie tickets upon enrollment and a $50 for every follow-up visit attended. Primary analyses will use intent-to-treat longitudinal models that will include outcomes from randomization through the time of dropout or 12 mo, whichever is longer. Secondary analyses will adjust models for baseline covariates that may be associated with loss to follow-up. We anticipate very few missing outcomes because weight and vital sign (medical stability) measures are SOC in AN care during hospital and at follow-up and the majority of patients hospitalized at our programs return to us for follow-up care. Reasons for refusal to participate will be collected from patients and families who decline enrollment.

C. Data Collection and Rationale for study measures: Other than the treatment we are testing (HCR vs. LCR), patients will receive SOC in the hospital. Thus, as shown in **Table 2**, the vast majority of procedures in hospital are SOC. Follow-up visits, on the other hand, are for the purpose of collecting data and will be scheduled at the designated time points. All questionnaires and interviews are provided in the **Appendix.**

C.1. Baseline Covariates: The following covariates will be collected upon admission prior to randomization.

(1) Demographics and eating disorder history: an intake form will be self-administered (with study coordinator as proctor, 15 min) to assess: highest body weight, lowest body, date of onset (to calculate length of illness and rapidity of weight loss), family history of eating disorder, self-reported race/ethnicity, maternal education and zipcode (to indicate socioeconomic status), date of birth.

(2) Eating Disorder Examination (EDE): is a standardized research interview that measures eating disorders psychopathology [58]. Dr. Le Grange (co-I, UCSF) has used this tool extensively in RCTs examining psychotherapeutic modalities and long-term recovery in AN and BN [59-61] and to categorize lower and higher risk study participants [62]. He will oversee the psychological aspects of this study, including training EDE interviewers at both sites, who will be blinded to the treatment assignment, and monitoring inter-rater reliability in an ongoing basis and retraining staff as necessary.

(3) Food recall: dietary intake for the day prior to hospital admission will be assessed with a 24-hr food recall by the Research RD and analyzed via Nutrition Data System for Research (NDS-R [63]) for total kcal and macronutrient profile. Dietary Density (DDS) and Variety Scores (DVS) will be calculated since acceptance of more energy dense and variety of foods in hospital has been shown to predict recovery at 8 mo [64].

(4) Severity of illness: %mBMI and HR on admission

C.2. Data Collection (see Table 2 for procedure schedule)

a. SOC in hospital: Participants will be followed daily in hospital. Consistent with SOC for these patients, night

time HR will be assessed with continuous cardiac monitoring throughout hospital stay, temperature will be measured orally and BP will be measured every 4-8 hr. Postural changes will be assessed with supine measurements (after 5 min), followed by standing measurements (after 2 min). When multiple vital signs measures are taken per protocol during one hospital day or one outpatient clinic visit, the lowest HR will be recorded. Weight is measured every morning upon waking after voiding on an electronic scale, with the subject wearing only a hospital gown. Height will be measured upon admit with wall-mounted stadiometer. Electrolytes will be monitored per SOC as described in **B.4.c**.

b. Study in hospital: Participants at both sites will complete the questionnaires above.

c. Study follow-up data: Participants will return for five study follow-up visits through 12 months post-randomization. Anthropometrics and vital signs: Height, weight and vital signs will be measured according to the in-hospital protocol by trained medical staff with standard equipment. Follow-up visits will be scheduled after school/work. Although this is not ideal for data collection, in our vast experience with adolescents it is good for feasibility and retention long-term. Afternoon weights are less accurate than in-hospital morning weights, however they will be comparable between follow-up visits beginning at dy 10. Vital sign measures will be taken after a 20-min rest to minimize the influence of activity required to attend the visit (e.g. walk from car). After resting, vital signs will be measured in the research center with standard, calibrated equipment and with postural changes according to the procedure above. Data will be entered directly into the electronic data capture system with fillable and constrained sections for anthropometric measures and vital signs to minimize error. Participants will complete these questionnaires:

(1) Follow-up form: This self-report form was developed as part of our National Eating Disorder Quality Improvement Consortium (NEDQIC) of 14 eating disorder programs. It will take 5 min to complete at all follow-up visits. The purpose is to document medications pertinent to recovery measures (menses and psychopathology), including medications, current mental health care, other medical and psychological/psychiatric care ("other care") outside of our medical centers (e.g. residential care, psychiatric hospitalization). Psychotherapy modality and adherence may be important prognostic covariates of long-term outcomes [30, 57, 65] in this open follow-up study.

(2) Health Care Utilization and Missed School (HCUMS) Survey: This questionnaire will draw from established tools to assess cost, however it will be tailored for AN and integrated with the follow-up form (above). In addition to to "other care", it assesses health care utilization since last study visit including medications, physician visits, dental visits, hospitalizations, ER visits and laboratory testing.

(3) Food records: Parents (or participants if > 18 yrs and living independently) will be educated on keeping 4-day records at home. The research RD will collect these at every follow-up visit, check them for completeness and send them to UCSF for analysis (as described for 24 hr recalls). These data will be used to prospectively track dietary intake during follow up, which could be associated with long-term effects.

C.3. Timing of Procedures: Table 2

	INPATIENT			OUTPATIENT FOLLOW-UP				
	Admit	Daily	DC*	Rnd+10 dy	Rnd+1 Mo	Rnd+3 Mo	Rnd+6 Mo	Rnd+12 Mo
MEDICINE/NURSING PROCEDURES								
Weight	SOC	SOC	SOC	X	X	X	X	X
Height	SOC			X	X	X	X	X
Vital Signs	SOC	SOC	SOC	X	X	X	X	X
Electrolyte monitoring ¥	SOC	X	SOC					
NUTRITION PROCEDURES								
24-hr food recall	X							
Patient educn--Food records			X					
4-day food record				X	X	X	X	X
QUESTIONNAIRE ADMINISTRATION								
EDE	X		X		X	X	X	X
HCUMS survey				X	X	X	X	X
Demogr & Eating Disorder history	X							
Follow-up form				X	X	X	X	X

* DC = discharge; SOC = Standard Of Care; Rnd = Randomization; ¥ SOC is every other day; we will monitor daily as part of Aim 2.

C.4. Safety

a. Medical Oversight: This study begins with a hospitalization as per SOC for patients who are medically unstable with malnutrition secondary to AN. Patients will be admitted to the adolescent medicine service if they are deemed medically unstable per published criteria [27]. Once admitted, patients will be eligible for study enrollment. The treatment (HCR or LCR) is limited to the hospital stay. Aside from the questionnaires at both sites and daily (instead of every other day) electrolyte monitoring, all hospital procedures are consistent with SOC. After discharge, participants will be followed openly. They are required to be under a physician's care to ensure medical stability but not required to receive that care from us (however many do). Many patients have a psychiatrist to manage psychiatric co-morbidities such as anxiety and depression. If they receive care or hospitalization elsewhere they can still continue in the study and we will collect that with our follow-up form (**see Appendix**)**.** If a participant becomes medically unstable and they refuse hospitalization against medical advice, they will be withdrawn from the study because continued outpatient treatment would be unsafe.

b. Prospective monitoring of AEs: Aim 2 specifies three electrolyte abnormalities that will be monitored prospectively in all participants and documented as described in **C.4.b.&c**: hypophosphatemia (≤3 mg/dL), 2B) hypomagnesaemia (≤1.7 mg/dL), and 2C) hypokalemia (≤3.5 mEq/L).

c. Independent Data Monitoring Committee (DMC): As a multi-center clinical trial comparing treatments, the proposed study is required to have an independent DMC according to the NICHD policy for clinical research monitoring. The purpose of the DMC is to ensure the safety of participants and validity of the trial. We will draft a DMC Charter using the NICHD template, the content of which is described in Human Subjects.

C.5 Statistical Methods

a. Projected pool of eligible participants and accrual rate: At Stanford, in 2012 there were 295 admissions to the dedicated inpatient eating disorders unit, with approximately 36% of patients meeting DSM-4 criteria for AN [66]; 100 similar patients were admitted at UCSF. With the broader eligibility criteria also including DSM-5, we anticipate at least 40% of patients (120 per yr at Stanford and 40 at UCSF) will be eligible. Of those who are eligible, we estimate that at least 50% will agree to participate and thus we will not attempt to achieve equal enrollment across sites. We will accrue 3-4 participants per mo over 3 yr until N=120 is reached [and retain 85% of this sample through 12 mo as shown in open follow-up studies of participants with AN [57].

b. Commitments of Site PIs, Research Teams, and Participants: Both site PIs have successfully recruited and retained AN participants in research projects and seen them to completion and publication. Furthermore, co-PI Hilton is a faculty biostatistician with extensive experience in clinical trials. She will lead the DCC, aiming to ensure the trial is designed, executed, and analyzed without bias. Patient incentives to participate will emphasize the value of their contributions to medical research and remuneration for their time (section **B.5**).

c. Data Analyses:

Sample Description: The study sample will be summarized and described (e.g., mean ± SD) by stratification factor and baseline covariates to confirm general balance by arm and data will be summarized for completeness of follow-up (e.g., length of stay, last visit).

Aim 1A: Primary efficacy outcome. A mixed-effects regression model, with random intercept and slope and stratified by study site will compare study arms with respect to achievement and maintenance of clinical remission defined as the combination of MBMI and EDE score at mo 1,3,6,12 (separate analyses below). The model will assume linear trends over log-transformed time in two periods (mo. 0-3 and 3-12), estimate mean (95% CI) remission rates within and between arms at mo 3 and 12, and test for statistical significance at mo 3. This model reflects the fluctuating nature of MBMI and EDE in AN and reflects our hypothesis that remission will be higher in HCR than LCR at 3 mo based on our preliminary data (**Fig 2**). Aim 1 models will be supplemented with (i) potential moderators at baseline (included in regression models as main effects and interactions with period and time), such as DSM-5 criteria and EDE thresholds of risk and (ii) potential mediators at follow-up (included as time-dependent covariates), such as food recall (DDS and DVS), healthcare utilization, or incidence of AEs. In addition, separate mixed-effects models will analyze continuous versions of MBMI, EDE and HR to describe longitudinal trajectories.

Aim 1B: Secondary efficacy outcome. Medical instability is primarily defined as bradycardia (daytime HR < 50 bpm or night time HR < 45 bpm), but also includes hypotension (BP <90/45 mmHg), hypothermia (< 36° C) and orthostasis (increase in HR > 20 bpm or decrease in systolic BP > 20 mmHg or decrease in diastolic BP > 10 mmHg from lying to standing) [27]. Because medical stability fluctuates in AN, we will use an analogous model to compare arms, daily in hospital and at mo 1,3,6,12. This model will assume linear trends over log-transformed time from admission to discharge, and discharge to mo 12. The model will estimate mean (95%

CI) medical stability rates within and between arms at dy 10 and mo 12, and test for significance at dy 10.

Aim 2. Safety: Cox regression models, stratified by study site, will compare rates of AE incidence by arm during hospitalization for the first of the following: 2A) hypophosphatemia (≤3 mg/dL), 2B) hypomagnesaemia (≤1.7 mg/dL), 2C) hypokalemia (≤3.5 mEq/L). Follow-up will be censored at discharge. The proportional hazards assumption will be examined and alternative models used if violated. The model will generate an estimate of the hazard ratio (95% CI) and a Kaplan-Meier cumulative incidence plot will display arm-specific cumulative incidence rates. Analogous exploratory models will estimate rates separately for each AE. These incidence estimates will serve as valuable benchmarks for future studies.

Aim 3. CE: A decision tree of treatment costs, AEs, health care utilized (including rehospitalizations), and remission will compare the CE between the two study arms. The main CE outcome is incremental cost per additional adolescent remitted. Health care utilization will be costed using national data sources such as acquisition costs for medications, Kids-HCUP for hospitalizations, CPT codes for physician visits and mental health visits, and internet based costs for lab tests. We will use 2014 US costs and not charges. Indirect costs including missed school and workdays will be assessed and costed using national estimates of wages and salaries of this age group from the Bureau of Labor Statistics, in order to estimate loss of leisure time (school) or salary time (work).

We will determine the incremental CE ratio (ICER) as:
ICER = $Cost_{LCR}$-$Cost_{HCR}$/Number $Recovered_{LCR}$-Number $Recovered_{HCR.}$
Effectiveness will also be indicated by cost of rehospitalizations avoided (ie, rehospitalizations in LCR-HCR). We will determine the net monetary benefit (NB) of each treatment option as: NB=Effectiveness X Willingness To Pay (WTP) – Cost. A positive difference in NB between treatments indicates CE. We will also calculate an acceptability curve to demonstrate how parameter uncertainty affects the likelihood of selecting the optimal treatment at a given WTP threshold. Cost of treatment will be determined by initial hospitalization and 12 mo follow-up costs (not charges) including AEs and rehospitalizations. The HCUMS follow-up survey will assess indirect costs such as lost school and/or work (wages) using national data sources (**see C.2.c.(2))**. Effectiveness will be determined per aim 1; ICER will also use time (incremental cost per additional day of recovery time over 12 mo).

d. Power and Sample-size Considerations:

Aim 1. Based on studies of AN remission [30, 67], **Table 3.A** shows that with N=60 per arm we have 80% power on 2-sided 0.05-level test to detect a 20% difference (8% vs. 28%) if data were cross-sectional (ρ=1). Our longitudinal data will allow detection of smaller effects, especially if the correlation among outcomes is low (ρ<0.8). We anticipate 85% retention and non-differential dropout by arm. Since rates of **medical stability** at dy 10 are also expected to differ by at least 12% (**Table 3.B**.), we will be adequately powered for Aim 1B.

Table 3.A Detectable differences in remission-rates:

ρ*	LCR	HCR	Mo-3 Diff
1.0	8%	28%	20%
0.8	14%	34%	20%
0.6	16%	34%	18%
0.4	18%	34%	16%
0.2	20%	34%	14%
0.1	22%	34%	12%

Table 3.B. Detectable differences in medical stability-rates

ρ*	LCR	HCR	Day-10 Diff
1.0	72%	92%	20%
0.8	66%	86%	20%
0.6	66%	84%	18%
0.4	66%	82%	16%
0.2	66%	80%	14%
0.1	66%	78%	12%

*correlation among 5 time points within participant

C.6. Data Management

a. DCC: Dr. Hilton at UCSF will lead the DCC, which will be autonomous and independent of the clinical sites. It will be housed in the UCSF department of Epidemiology & Biostatistics, which will be located on the Mission Bay campus of the University as of Sep 2014. The department is staffed primarily by statisticians and scientific researchers who conduct data-intensive research, collaborative data collection and analyses from multiple sites. They are equipped with an independent network of sophisticated and reliable computer systems with high-level security for protecting health information. The network is maintained by an in-house computer staff, which manages all aspects of the network, including ongoing maintenance, installation and upgrades of hardware, software and structural components such as cabling and servers. Dr. Hilton is the lead RCT biostatistician and routinely guides the work of Master-level statisticians, data managers and programmers. Dr. Hilton has coordinated trials for numerous previous and on-going NIH-funded studies, chairs multiple DMCs, and consults for FDA and pharmaceutical companies on trial design and analyses. Thus, UCSF has experience maintaining a distinctly separate but closely coordinated working relationship between clinical sites and data center.

b. Electronic data capture: Both clinical sites are equipped with the same Research Electronic Data Capture (REDCap) system for databases, data entry forms, online questionnaires and data validation. Data will be automatically exported to STATA for analysis using The Data Export Utility. The DCC uses advanced features including branching logic for dynamic data entry form generation, file uploading, data importing, and embedded calculated database fields.

c. Confidentiality: Loss of confidentiality is a recognized risk of participating in clinical research since protected health information, medical history, and demographics are used for the study. Loss of privacy may lead to problems with insurability or social stigmatization. We will make effort to minimize this risk and have systems in place to ensure confidentiality. Data will be de-identified and thereafter handled by ID number, rather than by name. No publications will include the names of patients or identifying information about study participants.

C.7. Project Feasibility: The proposed project is feasible for several reasons. First, our enrollment targets are feasible and historical treatment approaches are quite similar. Second, PIs at both clinical sites have developed the preliminary data leading up to the proposed project. Our work has spurred a new line of inquiry in this area; our most recent papers were published in a special issue of *J Adolesc Health* highlighting refeeding in AN. Furthermore, the PIs have worked together extensively to disseminate these results, build consensus in this area and educate fellow clinicians through collaborative presentations at six international conferences. Third, this work is already being translated into clinical practice and policy; we published a policy statement on hypophosphatemia in AN refeeding [68] and have a policy paper on medical management of AN in press [23]. Finally, co-PI Hilton, is a senior biostatistician with extensive experience in clinical trials to ensure that randomization, data collection, transfer and management are synchronized and rigorous.

C.8. Anticipated Limitations and Difficulties: As with any clinical study, enrollment is the first challenge. We examined feasibility carefully and included two sites to ensure that enrollment targets are met. We will have substantial outcome data that will allow us to detect meaningful differences upon discharge from hospital and at one year. A second known problem with multi-center studies is variability in trial conduct between sites, which we will actively minimize by: 1.) disseminating and pilot-testing protocols, 2.) using the DCC to produce randomization schemes for each site, to train personnel on electronic data capture and transfer, and to manage and analyze all data, 3.) training and recalibrating personnel on protocol execution, interviews, questionnaires and data collection, 4.) utilizing the same type of equipment at both sites when possible, and 5.) scheduling regular lab and PI meetings. Despite all of these efforts, the DCC will devise process measures that will allow monitoring of variability in trial conduct between sites and over time. A third problem is secular trends associated with the long enrollment period of this study, which may impact outcomes; however, the inclusion of the new atypical AN diagnosis will increase the generalizability of our findings. The final and largest limitation of the proposed study is that it is open-label (unblinded) and open follow-up. Participants will receive various mental health care during follow-up. Randomly assigned, protocolized mental health care would be ideal but is beyond the scope and budget of the proposed work. We expect this to influence 12 mo effects [69, 70] but to be distributed equally between arms. We will collect comprehensive data on mental and other healthcare utilization to adjust long-term effects and establish inclusion criteria for our future studies.

C.9. Timeline: Table 3

YEAR	YR 1		YR 2		YR 3		YR 4		YR 5	
MO	1-6	7-12	1-6	7-12	1-6	7-12	1-6	7-12	1-6	7-12
Training	X	*	*	*	*	*	*	*		
DSMB	X		X		X		X		X	
Lab Meetings	X	X	X	X	X	X	X	X	X	X
Enroll	0	20	20	20	20	20	20	0	0	0
1-yr Follow-up	0	0	20	20	20	20	20	20	0	0
Data	Refine systems		Collect/manage				Analyze			Write-up

* Regular retraining to control inter-rater variability

C.10. Future directions: The purpose of this multi-center RCT is to compare short- and long-term recovery in adolescents hospitalized with AN secondary to malnutrition and refed on LCR vs. HCR. The proposed study will provide evidence to develop recommendations for refeeding of patients with AN. The PIs are actively involved in policy-making within their professional organizations and will continue to disseminate this work widely [50]. We will build on this work with future studies of: 1.) The effect of dietary components on safety (such as carbohydrate load); 2.) Mechanisms to explain any differences in cognitive recovery (such as meal-time stress); 3.) Quality-of-life and cost-of-care decisions (such as re-engagement in peer networks).

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