

STUDY PROTOCOL

Official Title

Renewal of the Multi-center Randomized Controlled Trial of Refeeding in Anorexia Nervosa

Study

Individualized Study of Refeeding to Optimize iNpatient Gains (iStRONG)

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Individualized Study of Refeeding to Optimize inpatient Gains (iSTRONG)

Renewal of the Multi-center Randomized Controlled Trial of Refeeding in Anorexia Nervosa

A. OVERVIEW

The primary purpose of this trial is to compare the efficacy and safety of Individualized Caloric Refeeding (ICR) to the new standard of care, Higher Calorie Refeeding (HCR), in hospitalized patients with atypical anorexia nervosa (AAN).

We hypothesize that ICR will restore medical stability faster than HCR with no increase in electrolyte abnormalities. After hospitalization, the major barrier to care in AAN is lack of consensus on clinical remission and controversy over whether these formerly overweight patients should gain weight to recover. We will examine metabolic, hormonal and psychological markers during long-term follow-up, toward the goal of developing a definition of clinical remission in AAN. Based on our finding that Weight Suppression (WS) is a significant predictor of illness severity in AAN at admission, *we hypothesize that WS during follow-up represents incomplete recovery from AAN.*

AIM 1. Efficacy: We hypothesize that ICR will restore medical stability faster than HCR during hospitalization, defined as: 1.) heart rate (HR) ≥ 45 bpm, 2.) systolic blood pressure (SBP) ≥ 90 mmHg, 3.) temperature $\geq 35.6^{\circ}\text{C}$, 4.) orthostatic change in HR ≤ 35 bpm, 5.) orthostatic change in SBP ≤ 20 mmHg.

AIM 2. Safety: We hypothesize **no** evidence that ICR differs from HCR in *incidence of*: i) hypophosphatemia (<3 mg/dL), ii) hypomagnesaemia (<1.8 mg/dL), and iii) hypokalemia (<3.5 mEq/L) during hospitalization.

AIM 3. Clinical remission: **A.** We hypothesize greater improvements in %mBMI and EDE-Q score over 12-mo in ICR than HCR; and **B.** change in %mBMI will contribute to improvements in metabolic, hormonal, and psychological recovery markers (specified above); WS will modify these relationships.

B. DESIGN

- Study Design:** The purpose of this multi-center RCT is to compare ICR vs. HCR in hospitalized adolescents with AAN. *The trial is powered to detect a meaningful difference in time to restore medical stability.* Briefly, participants will be recruited upon hospital admission at UCSF and Stanford and randomly assigned to ICR or HCR, for a total sample of $N=74$. Treatments are not to 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 group assignment by simply viewing meal trays.
- Study population:** Inclusion criteria are age 12-24 yrs, DSM-5 criteria for AAN, and hospitalized with medical instability: 1.) night-time heart rate (HR) <45 bpm and/ or day-time heart rate (HR) <50 bpm, 2.) systolic blood pressure (SBP) <90 mmHg, 3.) Temperature $<35.6^{\circ}\text{C}$, 4.) orthostatic Δ HR >35 bpm, and 5.) orthostatic Δ SBP >20 mmHg. Patients with bulimia nervosa; current pregnancy, chronic disease (e.g. immune, renal disease), acute suicidality or psychosis, or hospital admissions for refeeding in the prior 6 mo. will be excluded.
- Randomization:** Participants will be stratified by site and randomly assigned within site 1:1 to ICR or HCR within 24 hrs of hospitalization. The Data Coordination Center (**DCC**) will produce a secure unpredictable allocation sequence and continually monitor balance between arms and sites.

C. PRE-ENROLLMENT SCREENING AND RECRUITMENT

*****Note on COVID-19 precautions**** Every effort will be made to modify clinical research protocols, including the recruiting and consenting process, to include telehealth-based conduct (e.g., conducting the informed consent discussion via Telehealth, collecting electronic signatures for consent). When clinical research must be carried out in person, it will be conducted by research personnel wearing a face mask per institutional policy and eye protection (e.g., eye shields, face shields, or safety glasses) according to UCSF Health PPE policy.*

1. **Determination of Eligibility**

When a newly admitted patient is identified on the Adolescent Medicine service, research staff will review the medical record to determine eligibility, and approach all eligible patients for enrollment within 24 hours of admission. If eligibility cannot be determined from the medical record alone, research staff will consult with the Adolescent Medicine interdisciplinary care team for further information. Research staff will attend inpatient rounds whenever possible, either in person or virtually, to gather as much pertinent information as possible related to the eligibility status of newly admitted patients before approaching for enrollment. In the rare case that a patient is later found to be ineligible (e.g. eating disorder diagnosis is later changed/updated by the psychiatry team), the patient will be immediately withdrawn from the study.

2. **Recruitment**

After confirming eligibility as described above in section 13.4, research staff will either enter the patient's room to recruit directly or, per COVID restrictions, contact the eligible patient or their parent over the phone or set up a telehealth visit to recruit them. The informed consent discussion will follow.

3. **Consent Process: Patients on the Adolescent Medicine Service**

Minor Participants (12-17 yrs): After confirming eligibility as described above, research staff will enter the patient's room to speak with a parent or, per COVID restrictions, contact the participant's parent over the phone to set up a telehealth visit. Research staff will conduct the informed consent discussion with the parent and child, allowing time for any questions and clarifications. The research staff will allow the parent and child to take time to decide whether to participate, and call back later to ask if they have made a decision. If remote, DocuSign will be used for signature.

If the parent is not English-speaking, an in-person or telephone interpreter through UCSF Interpreting Services will be employed for these conversations and interpreter number will be recorded.

Young Adult Participants (18-24 yrs): After determining eligibility as described above, research staff will enter the patient's room or, per COVID restrictions, contact the participant over the phone to set up a telehealth visit. Research staff will conduct the informed consent discussion with the patient, allowing time for any questions and clarifications. If remote, DocuSign will be used for signature.

4. **Consent Process: Parents or Guardians of hospitalized patients, to participate in Parent Questionnaires**

Parents of **Minor** Patients (12-17 yrs): If the parent consents for their child to participate in the main portion of the study, the informed consent discussion described above, the research staff member will additionally provide the parent information sheet related to the parent's participation and ask if they would like to participate in parent surveys.

Parents of **Adult** Patients (18-24 yrs): Parents of adult participants will be contacted only after becoming aware that participant is hospitalized. The study team will never be the first to let the parent know of their

adult child's hospitalization.

1. Young adult participant checks the box on the consent form to indicate "yes" we may contact their parent, and signs consent form.

2. Ask the hospitalized participant if their parent is already aware of participant's hospitalization.

3a. If YES: call parent, provide parent information sheet electronically, and review with them over the phone to obtain verbal consent from parent to complete Parent Questionnaire.

3b. If NO: inform participant that we will not contact parent until after participant has made parent aware of hospitalization. Arrange a time within a few hours to check in.

4. Call participant to ask if participant has informed parent of their hospitalization yet. This phone call should be documented in the Communication notes section of OnCore (under documents/info)

5a. If YES, call parent, provide parent information sheet electronically, and review with them over the phone to obtain verbal consent from parent to complete Parent Questionnaire.

5b. If NO, repeat from step 3b.

5c. If participant changes their mind, and decides that they do not want the research team to contact the parent, then this decision will be documented in OnCore, under the Consent tab. In this case, the parent will not be contacted and the participant will proceed with the study.

5. **Non-English-Speaking Parents**

We will only include English-speaking adolescent and young adult hospitalized patients with AAN. If **parents** of minor-age patients cannot speak English, we would still like to ask them to provide consent for their child to participate. This ensures that we will be able to capture the full diversity of our patient base here in the Bay Area. We will make use of in-person interpreters or telephone interpreters to review the consent form in detail with non-English speaking parents. We will have consent forms available in Spanish and English. To ensure full understanding before asking for consent, we will ask for signs of understanding and we will ensure ample time for questions is provided.

In addition to consenting for their minor children, there is a separate small role that we will ask **parents** of all hospitalized participants (with consent of the adult patients) to play in this study, involving a 7-minute parent questionnaire called the Parent-EDEQ. If parents of patients cannot speak English, the questionnaire may be provided in Spanish, or may be conducted as a proctored survey via an in-person or telephone interpreter for other languages. The survey measures parent perception of the child's eating disorder psychopathology, often yielding greater severity than endorsed by the adolescent or young adult, and will act as a secondary measure of ED psychopathology.

When consenting non-English speaking parents, we will employ the use of in-person or telephone interpreters through UCSF Interpreting Services. We will review the consent form in detail and record the interpreter number. We will ask parents to acknowledge understanding and ensure that there is ample time for questions. Similar strategies will be used when administering the 7-minute parent questionnaire as a proctored survey for non-English speaking parents to ensure that we record their questionnaire responses accurately.

If the parent's preferred language is Spanish, we will provide written materials in Spanish including the consent form and parent questionnaire.

D. STUDY PROCEDURES

	INPATIENT			OUTPATIENT FOLLOW-UP			
	Admit	Daily	DC*	3 Mo	6 Mo	9 Mo	12 Mo
Weight/Height/Vitals	SOC	SOC	SOC	X	X	X	X
Electrolyte monitoring ‡	SOC	SOC	SOC				
Questionnaires: e.g. EDE-Q	X		X	X	X	X	X
Quick text check-ins		X		X	X	X	X
Blood draws	X		X	X	X	X	X
Stool sample (UCSF only)	X		X				
Indirect Calorimetry (REE)	X		X	X	X	X	X
TOTAL STUDY TIME (min)	99	N/A	52	116	116	116	116

* **DC** = discharge; **SOC** = Standard of Care; ‡ SOC is every day until physicians decide risk of refeeding is low and every other day thereafter; we monitor daily as part of Aim 2 until day 7, and every other day thereafter

1. **Procedures** (see table above for timing):

- a. **Study groups:** Group A will receive individualized caloric refeeding (**ICR**), beginning with 50 kcal/kg (up to a maximum of 3000 kcal/d); group B will receive higher calorie refeeding (**HCR**), beginning at 2000 kcal/d; both groups will advance 200 kcal/d until reaching individualized caloric goal. The study diet assignment lasts the duration of the inpatient hospitalization and ends at discharge.
- b. **Refeeding intervention:** Our refeeding protocols are published and have been reproduced. The refeeding intervention lasts the duration of the inpatient hospitalization and ends at discharge. Briefly, meal-based refeeding is consistent with standard of care on the unit and includes 3 meals + 2-3 snacks/day, on bedside trays, in the presence of meal monitors (sitters) who observe intake of all nutrition and remain in the room for 20-30 min afterwards. Patients may drink a liquid supplement (formula) providing 1.5 kcal per mL (360 kcal per 240 mL can) to replace refused kcals, and if oral formula is refused then nasogastric tube feeding is offered. In our parent trial, none of the 120 participants required nasogastric feeding; tube feeding on our unit is rare. Pre-filled diet orders for ICR or HCR are embedded in the electronic medical record (EMR), signed by the attending physician and advanced per protocol, increasing by 200kcal/d to goal. Meals are prepared by hospital foodservice per U.S. Dietary Guidelines (~30-40% fat, 15-25% protein and 35-55% carbohydrate). Menus are continually analyzed via the hospital foodservice database (Software v.19.4, Computrition, Inc., Westhill, CA) to ensure conformance to this distribution as menu items are added or changed over time.

Blood draws (5 minutes): We are proposing six blood draws: twice in hospital and four times in follow-up. Daily, fasting blood draws in hospital between 5-7 am are Standard of Care (**SOC**) for the first 7 days, every other day thereafter, and more frequently if needed. These electrolyte monitoring blood samples provide the safety data for **AIM 2**. Additional blood samples for biomarkers and biobanking will be collected in hospital alongside the SOC blood draw. These samples will be drawn within 48 hrs of admission and discharge. To be consistent with the inpatient protocol, follow-up blood draws will be performed in the morning while fasting. All samples will be drawn and processed via a standardized protocol in the clinical laboratories, equipped with research cores staffed by phlebotomists trained in research specimens. Testosterone will be assessed with Enzyme-linked immunosorbent assay (ELISA); cortisol, E2, LH, FSH, and T3 are assessed by chemiluminescent immunoassay;

leptin is assessed by radioimmunoassay. The remaining volume will be stored for biobanking (see below) Over the course of the year, between 6.5 and 7.5 tablespoons (92mL – 107mL) of blood will be drawn. At admission and follow-up appointments, between 3 to 4 teaspoons (16mL – 19mL) of blood will be drawn. At discharge, about 2.5 (12mL) teaspoons of blood will be drawn.

- c. Biobanking serum and stool: Whole blood will be processed into serum and stored in cryovials. The samples will be sent to the UCSF Biorepository and Tissue Biomarker Laboratory (BIOS) for long-term storage at -80°C. These samples will be used for future analyses to support new directions in refeeding research, e.g. novel biomarkers.
Given the emerging role of the gut microbiome in refeeding, and since our patients are on strict bed rest in hospital, sometimes requiring bedside commode, the UCSF site will collect stool samples that would otherwise be wasted. Two cryovials of stool free from urine contamination will be obtained as close as possible to admission and discharge. Samples will be sent to BIOS for storage at -80°C until future analyses, including DNA isolation and nucleotide sequencing.
- d. Indirect calorimetry (30 minutes including rest): REE will be measured in the morning, while fasting and awake, following the blood draw and while lying comfortably. After 15-20 minutes of rest, the participant will breathe into the handheld indirect calorimeter for 10-15 minutes. We will use a handheld portable indirect calorimeter that has been validated against stationary equipment. This equipment calibrates on room air, avoiding the need for air tanks that prevent transport. It features a mouthpiece and nose clip instead of an enclosed breathing canopy, which improves comfort, and requires shorter breathing measurements, which will improve comfort as well.

The handheld indirect calorimeter measures oxygen consumption (VO₂) to calculate Resting Metabolic Rate (RMR). Output includes RMR, VO₂ and VCO₂ with a constant Respiratory Quotient (RQ) to examine fuel use (percent of carbohydrate vs. fat). The MedGem device (MicroLife Home Solutions, Golden, CO) measures oxygen consumption and determines RMR based on a constant RQ of 0.85. This is accomplished without measurement of CO₂ production. Under both normal and pathophysiologic conditions, it is extremely rare for a person to have a true metabolic RQ outside the range of 0.75 to 0.95. Within this range of RQs, the use of a constant RQ of 0.85 has a maximum error of only ±2.2%.

- e. COVID-19 PCR test: During the COVID-19 pandemic, institutional guidance will require us to provide a negative COVID-19 PCR test prior to engaging in any aerosol-generating procedures (negative results within 4 days prior to procedure). When required, participants will sign a consent addendum for the COVID-19 PCR test.
- f. Interviews and Medical History Data collection (35 min at baseline, 25 min at follow-ups): collected by CRC via medical record or interview with participant at baseline and follow-up as specified.
 - f.1. Demographics, eating disorder history and physical** (15 min): baseline information from the SOC physician examination and proctored questionnaire includes WS, pubertal stage, menstrual history, ASQ, medications (including hormonal contraceptives), family history of eating disorder, self-reported race/ethnicity, maternal education and zip code (socioeconomic status), date of birth. Menstrual history such as resumption of menses will continue to be collected throughout follow-up.
 - f.2. Growth records**: Growth records (height, weight and BMI curves) are obtained from Primary Care Providers as part of the referral packet to our eating disorder programs and used to evaluate weight history, WS, and other growth patterns that may predict response to refeeding and recovery targets.
 - f.3. Healthcare utilization form** (5 min): medications, mental health care, other care outside of our

medical centers (e.g. residential care), and readmissions collected as potential prognostic covariates of long-term outcomes in this open follow-up study and to assess cost-efficacy of the proposed treatment. Administered as a proctored interview, in conjunction with medical record review.

f.4. Diet recall and calorie counts (20 min): 24-hr food recall by the Research RD to assess dietary intake for the day prior to hospital admission and at each follow-up. Will be analyzed for total kcal and macronutrient profile as covariates of treatment outcomes via Food Processor (ESHA, v.11.1). In hospital, calories provided on meal trays and consumed are carefully tracked with calorie counts by Diet Technicians and nursing staff trained on protocol. These data provide proof of concept to demonstrate treatment fidelity and acceptability (formula intake to replace refused kcals)

- g. **Self-report questionnaires** (~33 min at admission, ~10 min at discharge, and ~26 min at follow-ups): collected in hospital and follow-up as specified, to be administered securely online and completed prior to or during study visits on laptop, phone or tablet.

g.1. Patient Health Questionnaire Depression Scale (PHQ-8, 2 min): a measure of depressive symptoms.

g.2. Eating Disorder Examination – Questionnaire (EDE-Q, 5 min): A self-report measure of ED psychopathology over 28 days, validated against gold- standard, 60 min interview and used as a recovery outcome.

g.3. The Generalized Anxiety Disorder 7-item Scale (GAD-7, 1 min): A standard measure of anxiety symptoms.

g.4. Modified Weight Bias Internalization Scale (WBIS-M, 2 min): measure of the degree to which individuals internalize negative stereotypes about their weight status at baseline and follow-up to examine changes in eating, weight and shape concerns, behavioral problems, and quality of life; relevant in AAN patients who may have experienced stigma at their pre-morbid higher weight.

g.5. Sociocultural Attitudes Towards Appearance Questionnaire-4 Revised (SATAQ-4R, 5 min): measure of societal influences on body image and eating disturbances and internalization of appearance ideals; at baseline and follow-up to examine changes in body image, disordered eating, personal acceptance and pursuit of thinness, relevant in AAN given higher weight individuals' nonconformity to the "thin ideal" and societal pressure.

g.6. The Body Image-Acceptance and Action Questionnaire (BI-AAQ, 2 min): measure of experiential avoidance of and flexibility with body image, at baseline and follow-up to examine changes in ED psychopathology, psychological distress, body image dissatisfaction, and disordered eating; relevant in AAN because body acceptance may be more challenging for higher weight individuals.

g.7. Subjective Units of Distress Scale (SUDS, 1 min): a single question asking the participant to rate their momentary distress on a scale of 0-100. We are using this to evaluate mealtime stress. The SUDS will be administered via text message each evening at dinnertime, for the duration of hospitalization.

g.8. The Distress Tolerance Scale (DTS, 2 min): a standard measure of distress tolerance, which may moderate the impact of refeeding condition on outcome.

g.9. Eating Disorder 15-item Scale (ED-15-Y, 2 min): a sensitive measure of change in eating disorder psychopathology with a short time frame that will allow us to capture changes during hospitalization.

g.10. Physical Activity Questionnaire (5 min): will be used to assess caloric expenditure in conjunction with our caloric intake/dietary assessment.

g.11. Abbreviated Acceptability Rating Profile (AARP, 2 min): a 8-item questionnaire that measures patient and caregiver-rated treatment acceptability and appropriateness. The instructions have been modified to refer to each treatment arm, and will therefore be completed twice (separately for each treatment).

g.12. Satisfaction with Services Scale (SSS, 2 min): a 5-item self-report measure of patient and caregiver satisfaction with the treatment they receive. The SSS specifically asks youth and caregivers to report on whether they perceive their needs and preferences were met, and it represents one type of treatment outcome. The questionnaire has been modified to examine satisfaction with nutrition services, as well as an added question regarding satisfaction with duration of hospitalization.

g.13. Treatment Preference & Perception – adolescent version (2 min): These items were generated to elicit treatment preferences from patients and their caregivers. The first section asks participants to state their treatment preference, and the second section assesses perceived treatment received (given that participants are blinded to treatment condition) from patients and their caregivers, including what treatment they think they received.

g.14. Subjective Units of Distress Scale (SUDS, <<1 min): This quick check-in mood survey will be administered by text message each evening at dinnertime during hospitalization and once at each follow-up timepoint to assess mealtime distress as a secondary outcome.

g.15. Car, Relax, Alone, Forget, Friends, Trouble (CRAFT, 1 min): Used for monitoring substance usage within adolescent populations. The CRAFT will be administered as part of standard of care upon admission to the inpatient unit at UCSF, and will be administered as an online survey upon admission.

h. **Parent questionnaires (15 min at admission, 10 min at discharge, and 10 min at follow-ups):** collected from parent or caregiver at baseline and follow-up as specified. Administered securely online.

h.1. Parent-EDE-Q (P-EDE-Q, 7 min) is a secondary measure of ED psychopathology, often yielding greater severity than endorsed by the adolescent.

h.2. Treatment Preference & Perception – parent version (2 min): The same preference and perception items will be assessed in the parent or caregiver.

h.3. Parents Versus Anorexia (PVA, 2 min): a 7-point parent self-report measure of parental efficacy about supporting their adolescent when they participate in family-based treatment.

h.4. Parent Version of Eating Disorder 15-item Scale (P-ED-15, 2 min): evaluates parent perception of short-term changes in eating disorder psychopathology and is based on the ED-15.

h.5. Satisfaction with Services Scale (SSS, 2 min): a 5-item self-report measure of patient and caregiver satisfaction with the treatment they receive. The SSS specifically asks youth and caregivers to report on whether they perceive their needs and preferences were met,

2. Retention and Attrition

- a. While research is voluntary and participants may choose to withdraw at any time, we achieved 88% retention with a similar design and timeline in StRONG, which is excellent compared to other open follow-up studies of AN. Data completeness is bolstered by overlapping the majority of study measures (e.g. weight, blood draws) with SOC when possible and the fact that 70% of study participants receive their follow-up care with us. Active retention includes phone calls, emails, newsletters and birthday cards. We also developed systems to collect data for patients who receive care elsewhere and miss their study-specific visits, with IRB-approved release of information forms from primary care providers and/or residential treatment facilities, and permission for home visits to measure height and weight. Questionnaires are administered online (Qualtrics ©) with a text reminder system including a link to the survey, which can be completed on a smart phone, laptop or iPad. We budgeted for \$100 incentives at admission and follow-ups to compensate for blood draws and additional time for indirect calorimetry (see table above). Reimbursement for gas will be provided if the participant is traveling over 50 miles roundtrip to the site. Parking validation will be provided for all participants at study follow-up visits only. While we strive to retain as many participants as possible, research is voluntary,

and participants may change their mind or withdraw from the study at any time. If the participant indicates they are no longer interested in participating, then all procedures and all retention efforts will end immediately.

E. STATISTICAL METHODS

1. Projected pool of eligible participants and accrual rate: For the parent trial, StRONG, we approached N=301 eligible patients and enrolled ~3-4 participants/mo. For a total of N=120, including N=51 with AAN. For the proposed trial, i-STRONG, we will enroll N=74 patients with AAN. Systems for the current trial are in place to allow us to begin enrollment immediately after our IRB approval and funding is in place. We will accrue ~2 participants/mo. Over 3 yr until target enrollment is reached. We will retain 88% of participants over 12 mo. As we did in the parent trial.

Data Analysis:

AIM 1. Efficacy: We hypothesize that ICR will restore medical stability faster than HCR during hospitalization, defined as: 1.) heart rate (HR) ≥ 45 bpm, 2.) systolic blood pressure (SBP) ≥ 90 mmHg, 3.) temperature $\geq 35.6^\circ\text{C}$, 4.) orthostatic $\Delta\text{HR} \leq 35$ bpm, 5.) orthostatic $\Delta\text{SBP} \leq 20$ mmHg.

Primary efficacy outcome (Aim 1): Time to restore medical stability will be adjudicated by a five-point index: 1.) 24- hour HR ≥ 45 bpm, 2.) SBP ≥ 90 mmHg, 3.) temperature $\geq 35.6^\circ\text{C}$, 4.) orthostatic increase in HR ≤ 35 bpm, 5.) orthostatic decrease in systolic BP ≤ 20 mmHg. Each criterion will be scored as “1” if met, “0” if unmet and missing (not scored) if not measured. Medical stability will be considered restored when all criteria are stable for 24 hours, allowing a maximum of one missing value (i.e. participants will be considered stable if meeting 4/4, 5/5 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. In the parent study most but not all participants met full stability criteria by hospital discharge (~85%), therefore we will plan to use survival analysis to allow right-censoring. As in the parent study, we expect randomization to balance distributions of baseline covariates, however we will confirm this with box plot, bar graph and descriptive statistics. If balanced, log rank test will compare time to achieve medical stability by arm while accounting for the correlation within sites. If unbalanced, Cox proportional hazard ratio model will be used to control for potential bias due to the confounders. Secondary efficacy outcomes will include proportion achieving medical stability, change %mBMI vs. baseline, and time to restore HR.

AIM 2. Safety: We hypothesize no evidence that ICR differs from HCR in *incidence of*: i) hypophosphatemia (<3 mg/dL), ii) hypomagnesaemia (<1.8 mg/dL), and iii) hypokalemia (<3.5 mEq/L) during hospitalization.

The occurrence of the aEs during hospitalization will be summarized with frequencies, percentages and 95% confidence intervals, and compared between treatment arms with Fisher’s exact test. These outcomes will be actively minimized by study physicians; we expect few aEs to occur.

AIM 3. Clinical remission: A. We hypothesize greater improvements in %mBMI and EDE-Q score over 12-mo in ICR than HCR; and **B.** change in %mBMI will contribute to improvements in metabolic, hormonal, and psychological recovery markers (specified above); **WS will modify these relationships.**

Aim 3A. Primary analysis for Aim 3 will compare clinical remission components over 12-mo in ICR to HCR, with (generalized) linear mixed effect models (GLMM for EDE-Q, LMM for %mBMI). Models

will include time, treatment (ICR vs. HCR), and time×treatment interaction while controlling for any unbalanced baseline covariates. We will include study sites and patients as random effects to account for correlation within clusters. Assuming similar background effects/trends over time for both groups, the time×treatment interaction will provide us a mITT estimate for the effect of ICR vs. HCR on clinical remission parameters over time.

Aim 3.B. LMM and linear mixed-effect lag models (LMLM) will respectively evaluate the impact of Δ %mBMI on contemporaneous and subsequent changes in metabolic (REE, T3), hormonal [ROM, LH, FSH, E2 (girls); testosterone (boys); leptin; cortisol], and psychological recovery (EDE-Q, BI-AAQ, WBIS-M, SATAQ-4R) over 12 mo. LMM will have recovery markers as outcomes, include time, %mBMI, and time×%mBMI interaction as fixed effects, with site and patients as random effects. LMLM will replace concurrent %mBMI with last %mBMI for its effect on the subsequent recovery markers. If the relation between %mBMI and recovery markers varies over time, both the main effect of %mBMI and time×%mBMI interaction will be used to assess the %mBMI- recovery markers relation over time. Secondary analyses will explore WS and other baseline characteristics (e.g. pubertal stage, psychiatric medication) as potential moderators. Since ~90% will be female, we do not expect meaningful gender differences. To further understand whether weight gain is sufficient, we will assess the shape and magnitude of the Δ %mBMI and recovery markers over time. A significant positive relation will indicate a positive impact of weight gain on recovery; a plateau in biomarkers within published pediatric reference ranges or published norms for psychological measures will indicate that sufficient %mBMI was achieved. Additionally, to examine the mechanism of treatment on recovery, mediation analyses will consider direct and indirect effects of treatment around and through weight gain on recovery markers. The step-down procedure will be used to adjust for group comparisons on the multiple outcomes.

2.

- a. Missing and Drop out: We will minimize missing data as in the parent study: of N=1197 measures, we missed 0% of the HR, 0% BP, 4% Temp, 5% orthostatic BP, 7% orthostatic HR, 3% weight and 1% labs. We will assess completers and dropouts for differences in baseline characteristics; any differences will be used as covariates for adjustment in models. GLMM assumes data are missing at random, a less stringent assumption than missing completely at random, and uses all available data in analyses rather than using only complete case data. Sensitivity analyses will assess whether patients who withdrew prior to receiving treatment: 1.) differ from the mITT population by baseline covariates; and 2) change results of mITT analyses when included.

Power and Sample-size Considerations: This study is powered to detect a significant difference in time to medical stability between ICR and HCR (AIM 1), based on findings from the parent trial. This aim is executed in hospital and therefore we do not experience attrition [patients cannot leave unless against medical advice with signed legal documentation by parent(s).] However, 6% of randomized participants did withdraw prior to receiving treatment in the parent trial. Treatment effect for the proposed test group was estimated from StRONG participants with AN treated with HCR (mean 49 kcal/kg), approximating ICR, vs. AAN. N=34 per arm would provide 80% power on a 2-sided 0.05-level test to detect the expected difference in time to medical stability between ICR vs. HCR of 3.85 days (95% CI 1.09, 6.62). We will plan for a total sample of N=74 to allow for withdrawals and loss to follow-up. We will retain 88% of participants over 12 mo. as we did in the parent trial.

Aim 1: *This study is powered to detect a significant difference in time to medical stability between ICR and HCR, based on findings from the parent trial.* This aim is executed in hospital and therefore we do not experience attrition [patients cannot leave unless against medical advice with signed legal documentation by parent(s).] However, 6% of randomized participants did withdraw prior

to receiving treatment. Treatment effect for the proposed test group was estimated from StRONG participants with AN treated with HCR (mean 49 kcal/kg), approximating ICR, vs. AAN. N=34 per arm would provide 80% power on a 2-sided 0.05-level test to detect the expected difference in time to medical stability between ICR vs. HCR of 3.85 days (95% CI 1.09, 6.62). We will plan for a total sample of N=74 to allow for withdrawals and loss to follow-up (see **Aim 3**).

Aim 2: Outcomes for this aim are monitored closely as aEs and actively minimized through careful medical monitoring and protocolized correction (oral electrolyte replacement). [This aim is not powered.]

Aim 3A: Given the estimates from StRONG, 0.65 intraclass correlation of %mBMI at discharge, 3, 6, and 12 mo, standard deviation of 12%, and 88% retention, a starting N=74 over 4 follow-ups will provide 80% power in two-sided tests with a type I error level of 5% to detect a 7.6% group difference in %mBMI. For context as to how this may relate to the proposed recovery markers, in StRONG the difference in %mBMI in AAN participants with and without return of menses (ROM) was 102.6 ± 12.2 vs. 95.0 ± 3.4 %; in a larger study, Stanford site PI Golden found 106.1 ± 11.7 vs. 94.2 ± 8.9 %.

b.

F. DATA & SAFETY MONITORING PLAN

1. **Medical Oversight:** This study has heavy medical oversight because it begins in hospital with patients who are medically unstable. The treatment (ICR or HCR) is limited to the hospital stay; HCR is the current SOC at both clinical sites. Most hospital procedures are consistent with SOC, except for the questionnaires, REE measures and additional blood volume. Stool samples will be collected during the hospitalization from either the commode collection container. When possible, blood samples in hospital will be added to the existing daily blood draws that are SOC for electrolyte monitoring and performed by in-house phlebotomists. At follow-up visits, participants will have blood drawn at pediatric clinical research center and housed within our respective outpatient clinics at UCSF and Stanford. Blood draws do carry a small additional risk and indirect calorimetry can be uncomfortable, which will be clearly explained on the IRB-approved consent/assent forms. Study participants are followed openly while under a physician's care to ensure medical stability, with most receiving that care from us. Many patients have a psychiatrist to manage psychiatric co-morbidities. If they do receive care elsewhere, that information is collected via our questionnaires, and they can continue in the study. Participants who become medically unstable during follow-up will be offered readmission to hospital and receive SOC (not study diet).
2. **Safety monitoring:** The Data Coordinating Center (DCC), headed by Jing Cheng (Biostatistician), will review all data for safety, quality, completeness, and enrollment on an ongoing basis.

During treatment period (hospitalization): Clinical data will be thoroughly monitored for adverse events on a weekly basis. All serious adverse events will be documented, and those that are related to the study treatment will be reported to the IRB and NICHD on an ongoing basis. Mild and moderate adverse events that are specifically related to the refeeding treatment will be documented and collated for review at annual Data and Safety Monitoring Board (DSMB) meetings. While under the care of physicians in the hospital, electrolyte-related adverse events will be corrected with oral electrolyte supplementation per study protocol.

Electrolyte Replacement Protocol

*****Do NOT treat declining electrolytes in the normal range *****

Hypokalemia

K 3.1 -3.4 mmol/L	Extended release KCl 20 mEq PO; Recheck 8-12 hrs
K 2.5 -3.0 mmol/L	Extended release KCl 40 mEq PO; Recheck 8-12 hrs
K 2.2 -2.4 mmol/L	Extended release KCl 40 mEq PO STAT; Recheck 4 hrs & 12 hrs
K < 2.2 mmol/L	IV KCl; contact PICU

Hypophosphatemia

Phos 2.5 -2.9 mg/dL	Phos-NaK 1 packet (250 mg) TID
Phos 2.0 -2.4 mg/dL	Phos-NaK 2 packets (500 mg) TID
Phos < 2.0 mg/dL	IV Na-K-Phos 0.24 mmol/kg; max 15 mmol/dose; contact PICU

Hypomagnesemia

Mg 1.3 -1.7 mg/dL	Mag-oxide 1 tablet (133-200mg elemental Mg each) BID
Mg 1.0 -1.2 mg/dL	Mag-oxide 2 tablets (133-200mg elemental Mg each) BID
Mg < 1.0 mg/dL	IV Mg-SO ₄ @50mg/kg; max 2g/dose; contact PICU

Screening for suicidality and self-harm: Suicidality is a known comorbidity of atypical anorexia nervosa and contributes to the high mortality rate of this mental illness. It is also a known problem in the general adolescent and young adult population and therefore, suicidality screening is standard of care in both inpatient and outpatient Adolescent Medicine services. For the proposed study, we will employ the protocol developed for the parent study and consistent with standard of care, as described below. Per standard of care, all patients admitted will be screened for suicidal ideation with the National Institute of Mental Health's Ask Suicide-Screening Questions (ASQ) Toolkit. Additional self-harm questions have been added to the screen. A positive ASQ screen or self-harm screen will trigger additional precautions on the unit, depending on the risk category assigned: a) High Risk (red): Acute Positive ASQ Screen (regardless of Self Harm screen status) b) Moderate Risk (yellow): Non-Acute Positive ASQ Screen, or c) Positive Self Harm Screen (blue).

Each risk category triggers a corresponding automatic order-set within the electronic medical record, including consultation with Pediatric Psychiatric Consult Liaison Service, suicide/safe room precautions (e.g. removing dangerous objects, long cords, phones from the hospital room), paper plates and plastic cutlery on meal trays, 24-hour safety attendants, 5150 psychiatric hold if needed, and other standard of care precautions as deemed necessary by the inpatient medical and psychiatric care teams. For Non-Acute Positive ASQ Screens (yellow), social work will be consulted to do an in-depth screen based on the ASQ Worksheet to determine additional risk factors for suicide and self-harm, or to clear them of risk mitigation interventions. Acute positive ASQ screens (red) will be excluded from participating in the study, while non-acute positive (yellow) and self-harm positive (blue) screens will be allowed to participate. Passive suicidality and severe depression may still be present, or may develop after the initial screen, which will be monitored during the hospitalization per standard of care by the clinical team, and will be documented and recorded by the study team, and reported as adverse events if applicable.

During follow-up period: The treatment effect window ends at discharge from the hospital. Any adverse events that occur after discharge will not be deemed related to the study treatment. Only suicide attempts and suicidal ideation with an active plan will be reported to the IRB and NICHD. Other serious adverse events that occur during follow-up will be documented and compiled for review at annual DSMB meetings.

3. DSMB Reviews: In annual DSMB review meetings, the DCC will present data on enrollment, retention, and data collection in an open session with Drs. Garber, Golden and other Investigators. In a closed session (after investigators stepped out/signed off), the DCC will review safety and data quality by treatment arm. The Board will provide feedback and sign a completion report, which will be forwarded to the NICHD Project Officer. Finally, the Board will provide feedback on the data that they will wish to review at their subsequent meetings, which may include data on: demographics and comorbidities; recruitment, screening, refusals, exclusions, drop outs, withdrawals and reasons; visit attendance; subsequent hospitalizations (for any reason); adverse events (AE); prevalence and incidence of electrolyte abnormalities. The DSMB will be informed of serious adverse events that may be related to study treatment within 10 days of any such occurrence, and if necessary they will convene for interim videoconferences.
- a. Co-Investigator Anna-Barbara Moscicki was Vice-Chair for Clinical and Translational Research for the Department of Pediatrics at UCSF and is now Chair of Adolescent Medicine at UCLA. She will act as the liaison between the clinical care team and the clinical research team. In this role, she will also oversee the safety aim of the study and adherence to the Data Safety Monitoring Plan. She will train the study sites on the electrolyte monitoring and supplementation protocol, and reporting of adverse events. The physicians providing day-to-day medical oversight for study procedures and participants are Drs. Buckelew (UCSF) and Kapphahn (Stanford).
 - c.2. The DSMB oversight board members have professional expertise in eating disorders and biostatistics but are not investigators on the study: Loris Hwang, MD of the University of California Los Angeles, Rollyn Ornstein, MD of Penn State Hershey Children's Hospital, and Dylan Small, PhD of the University of Pennsylvania Wharton. Dr. Hwang and Dr. Ornstein have expertise in the medical management of atypical anorexia nervosa, with extensive experience in conducting clinical trials in this area of research. Dr. Small is a biostatistician and professor of Statistics, who has experience serving on data and safety monitoring boards for clinical trials. If selected for funding, we will add an expert on metabolic and hormonal biomarkers in AN to our current DSMB and convene the group prior to the start of enrollment.
 - b. Anticipated AEs: the risk factors for the refeeding syndrome have been well described in this patient population during refeeding, and do not present a study-specific risk. These symptoms are routinely managed as part of standard of care and will be managed in study patients with a standardized electrolyte supplementation protocol during the treatment period. The minimum thresholds whereby these AEs would be considered serious AEs (and reportable) are listed in the attached Appendix.
 - c. Procedures for communicating the outcome of DSMB reviews to the IRB & the study sponsor: Following annual DSMB meetings, the board members may request to see any additional data to make further assessments of acceptability of the safety of the trial. The DCC will prepare any requested data and send to the DSMB within 30 days. If the DSMB does not identify any safety or other protocol-related concerns within 30 days after a DSMB meeting, the DSMB will prepare and sign a summary report and submit it to the NICHD Project Officer, stating that:
 - A review of outcome data, adverse events, and information relating to study performance across all centers took place; the observed frequency of adverse events did not exceed what was expected and indicated in the informed consent;
 - A review of recent literature relevant to the research took place; and
 - The DSMB recommended that the study continue without modification of the protocol or informed consent.

If concerns are identified, the report to the clinical centers will outline those concerns, the DSMB discussion of the concerns, and the basis for any recommendations that the DSMB makes in response to the concerns. The report will be distributed by the Chair to each clinical center involved in the study. It is the responsibility of each clinical center to forward this information to the IRB.

The DSMB will first report to the DCC, who will inform the study PIs and NICHD Project Officer. If the PIs are notified of an AE or other external event meeting reporting requirements, it will be reported to the UCSF IRB within 10 working days.

- d. Study Stoppage: The DSMB has authority to recommend changes or stop the study due to safety or efficacy concerns. For example, if serious AEs are found to occur at differing rates in the treatment groups at any point, this would be grounds for stopping the study.

Anticipated Adverse Event	Mild - Grade 1 (not reportable)	Moderate - Grade 2 (not reportable)	Severe - Grade 3 (Reportable to IRB and NICHD; and will discuss with DSMB)
Specifically related to study aims (will document all levels and review with DSMB)			
Hypokalemia	3.1 - 3.4 mmol/L	2.5 - 3.0 mmol/L	<2.5 mmol/L
Hypomagnesemia	1.3 - 1.7 mg/dL	0.9 - 1.2 mg/dL	<0.9 mg/dL
Hypophosphatemia	--	2.5 - 2.9 mg/dL	<2.5 mg/dL
Hypotension	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Medical intervention indicated
Postural hypotension (orthostatic hypotension)	Change from lying to standing in HR $\geq$ 35 bpm; change in systolic BP $\geq$ 20 mmHg; change in diastolic BP $\geq$ 10 mmHg (hospitalization criteria)	Change from lying to standing in HR $\geq$ 60 bpm; change in systolic BP $\geq$ 20 mmHg; change in diastolic BP $\geq$ 10 mmHg	Change from lying to standing in HR $\geq$ 75 bpm; change in systolic BP $\geq$ 30 mmHg; change in diastolic BP $\geq$ 20 mmHg
Prolonged QT (Electrocardiogram QT corrected interval prolonged)	QTc 450 - 480 ms	QTc 481 - 500 ms	QTc $\geq$ 501 ms on at least two separate ECGs
Sinus bradycardia	36 - 40 bpm	30 - 35 bpm	<30 bpm; medical intervention indicated
Hypothermia	35.1 - 36.0 C (hospitalization criteria)	31.9 - 35.0 C	$\leq$ 32.0 C
Suicidal Ideation	Increased thoughts of death but no wish to kill oneself	Suicidal ideation with no specific plan or intent	Specific plan to commit suicide or attempt
Psychological Distress	--	--	Severe abnormal or excessive response; limiting self care ADL; inconsolable
Anxiety	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL
Psychiatric disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; disabling; limiting self care ADL
Depression	Mild depressive symptoms	Moderate depressive symptoms; limiting instrumental ADL	Severe depressive symptoms; limiting self care ADL
Other anticipated AEs; unrelated to our study aims (will only record SEVERE events)			
Dizziness with standing	Mild unsteadiness or sensation of movement;	Moderate unsteadiness or sensation of movement; limiting instrumental ADL	Severe unsteadiness or sensation of movement; limiting self care ADL
Dyspnea	Shortness of breath with moderate exertion	Shortness of breath with minimal exertion; limiting instrumental ADL	Shortness of breath at rest; limiting self care ADL
Pericardial effusion	--	Asymptomatic effusion size small to moderate	Effusion with physiologic consequences
Peripheral, sacral, or other localized edema	Localized to dependent areas, no disability or functional impairment	Moderate localized edema and intervention indicated; limiting instrumental ADL	Peripheral edema extending to the abdomen requiring medication to alleviate symptoms
Presyncope	--	Present (e.g., near fainting)	--
Pressure Ulcer	Pressure Ulcer Class 1 documented in EMR: Combined area of ulcers <1 cm; nonblanchable erythema of intact skin with associated warmth or edema	Pressure Ulcer Class 2: Combined area of ulcers 1 - 2 cm; partial thickness skin loss involving skin or subcutaneous fat	Pressure Ulcer Class 3 or above: Combined area of ulcers >2 cm; full-thickness skin loss involving damage to or necrosis of subcutaneous tissue that may extend down to fascia
Pulmonary edema	Radiologic findings only; minimal dyspnea on exertion	Moderate dyspnea on exertion; medical intervention indicated; limiting instrumental ADL	Severe dyspnea or dyspnea at rest; oxygen indicated; limiting self care ADL
Syncope/Fainting	--	--	Fainting; orthostatic collapse
Ventricular arrhythmia	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Medical intervention indicated
Cardiac disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; prolongation of hospitalization indicated; disabling; limiting self care ADL
Abdominal distension	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; limiting instrumental ADL	Severe discomfort; limiting self care ADL
Abdominal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL

Bloating	No change in bowel function or oral intake	Symptomatic, decreased oral intake; change in bowel function	--
Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas; limiting instrumental ADL	Obstipation with manual evacuation indicated; limiting self care ADL
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of >=7 stools per day over baseline; incontinence; prolonged hospitalization indicated; limiting self care ADL
Dry mouth	Symptomatic (e.g., dry or thick saliva) without significant dietary alteration; unstimulated saliva flow >0.2 mL/min	Moderate symptoms; oral intake alterations (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1 to 0.2 mL/min	Inability to adequately aliment orally; tube feeding or TPN indicated; unstimulated saliva <0.1 mL/min
Dyspepsia	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; surgical intervention indicated
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or prolonged hospitalization indicated
Vomiting	1 - 2 episodes (separated by 5 minutes) in 24 hours	3 - 5 episodes (separated by 5 minutes) in 24 hours	>=6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN, or prolonged hospitalization indicated
Alanine aminotransferase	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 x ULN
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L
Aspartate aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 x ULN
Dehydration	Increased oral intake indicated; dry mucous membranes; diminished skin turgor	IV fluids indicated <24 hrs	IV fluids indicated >24 hours
Hypercholesterolemia	>ULN - 300 mg/dL; >ULN - 7.75mmol/L	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L	>400 mg/dL; >10.34 mmol/L
Hyperkalemia	5.2 - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 mmol/L
Hypermagnesemia	2.5 - 3.0 mg/dL	--	>3.0 mg/dL
Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 mmol/L; hospitalization indicated
Hyperphosphatemia	5.0 - 5.5 mg/dL	5.6 - 6.0 mg/dL	>6.0 mg/dL
Hypertriglyceridemia	150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L	>300 mg/dL - 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L	>500 mg/dL ; >5.7 mmol/L
Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L
Hypoglycemia	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 mg/dL; <2.2 mmol/L
Hyponatremia	<LLN - 130 mmol/L	--	<130 mmol/L
Acute Food Refusal (Undefined in CTCAE)	--	Requiring feeding tube placement	Requiring tube feeding for 100% of calories for >3 days
Agitation	Mild mood alteration	Moderate mood alteration	Severe agitation; limiting self care ADL
Confusion	Mild disorientation	Moderate disorientation; limiting instrumental ADL	Severe disorientation; limiting self care ADL
Delirium	Mild acute confusional state	Moderate and acute confusional state; limiting instrumental ADL	Severe and acute confusional state; limiting self care ADL; prolonged hospitalization indicated
Headaches	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL
Insomnia	Mild difficulty falling asleep, staying asleep or waking up early	Moderate difficulty falling asleep, staying asleep or waking up early	Severe difficulty falling asleep or waking up early with medication and resulting in 3 days without sleep
Irritability	Mild; easily consolable	Moderate; limiting instrumental ADL; increased attention indicated	Severe abnormal or excessive response; limiting self care ADL; inconsolable
Panic attacks	--	--	Severe abnormal or excessive response; limiting self care ADL; inconsolable
Psychological Distress	--	--	Severe abnormal or excessive response; limiting self care ADL; inconsolable
Psychosis	Mild psychotic symptoms	Moderate psychotic symptoms (e.g., disorganized speech; impaired reality testing)	Severe psychotic symptoms (e.g., paranoid; extreme disorganization)
Restlessness	--	--	Severe symptoms requiring physical restraints