

Family-Based Interoceptive Exposure for Avoidant Restrictive Food Intake Disorder

PI: Robyn Sysko, Ph.D.

NCT06110806

Document Date: 4-30-2024

Family-Based Interoceptive Exposure for Avoidant Restrictive Food Intake Disorder

Study Chairman or Principal Investigator: Robyn Sysko, PhD

**Supported by:
The National Center for Complementary and Integrative Health**

Study Intervention Provided by: 1R34AT012194-01A1



Tool Revision History

Version Number: Version 1.2

Version Date: July 20th NCCIH response

Summary of Revisions Made: Updates based on feedback from NICCH, including:

- clarification of recruitment numbers, age range, exclusion for blindness or epilepsy if exposure to flashing lights at certain intensities or to certain visual patterns can trigger seizures, phase I and phase II timing and relationship to dose optimization, definition of maximum functional change, scheduling of sessions, timing of notification regarding comorbid diagnoses, potential benefits, prohibited interventions, monitoring of self-harm, suicidal ideation, or homicidal ideation, definition of adverse events, reporting changes in medical condition, follow-up of adverse events, safety planning, and analytic plan (e.g., convergence, covariance, power for DSEM, missing data).
- addition of parent exclusions, definition of substance dependence, description of parental role in treatment, general risks (e.g., with PII/PHI disclosure, communication with outside medical professional, access to database), explicit statement regarding disclosure of neglect or abuse per state laws, study physician name

If a change was not made in response to a comment, the comment is retained in this document.

Version Number: 2

Version Date: September 19, 2023

Summary of Revisions Made:

- Clarified time points of measures that needed to be created or adapted.
- Added information to the medical clearance form related to medical clearance assessment.

Version Number:

Version Date:

Summary of Revisions Made:

Version Number:

Version Date:

Summary of Revisions Made:



TABLE OF CONTENTS

| | <i>Page</i> |
|--|-------------|
| Tool Revision History..... | 2 |
| TABLE OF CONTENTS | 4 |
| STUDY TEAM ROSTER | 7 |
| PARTICIPATING STUDY SITES | 7 |
| PRÉCIS..... | 7 |
| 1. STUDY OBJECTIVES | 9 |
| 1.1 Primary Objective..... | 9 |
| 1.2 Secondary Objectives | 9 |
| 2. BACKGROUND AND RATIONALE | 10 |
| 2.1 Background on Condition, Disease, or Other Primary Study Focus | 10 |
| 2.2 Study Rationale..... | 12 |
| 3. STUDY DESIGN | 13 |
| 4. SELECTION AND ENROLLMENT OF PARTICIPANTS..... | 14 |
| 4.1 Inclusion Criteria | 14 |
| 4.2 Exclusion Criteria | 15 |
| 4.3 Study Enrollment Procedures | 15 |
| 5. STUDY INTERVENTIONS | 17 |
| 5.1 Interventions, Administration, and Duration | 17 |
| 5.2 Handling of Study Interventions..... | 21 |
| 5.3 Concomitant Interventions..... | 21 |
| 5.3.1 Allowed Interventions | 21 |
| 5.3.2 Required Interventions..... | 21 |
| 5.3.3 Prohibited Interventions..... | 21 |
| 5.4 Adherence Assessment | 21 |
| 6. STUDY PROCEDURES | 21 |
| 6.1 Schedule of Evaluations | 21 |
| 6.2 Description of Evaluations | 22 |
| 6.2.1 Screening Evaluation | 22 |
| 6.2.2 Enrollment, Baseline, and/or Randomization | 24 |
| 6.2.4 Followup Visits..... | 25 |



| | | |
|------------|--|-----------|
| 6.2.5 | Completion/Final Evaluation..... | 26 |
| 6.2.6 | Compensation: | 26 |
| 6.2.7 | End-of-Study Definition | 26 |
| 7. | SAFETY ASSESSMENTS..... | 27 |
| 7.1 | Specification of Safety Parameters | 27 |
| 7.2 | Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters | 27 |
| 7.3 | Adverse Events and Serious Adverse Events | 27 |
| 7.4 | Reporting Procedures..... | 29 |
| 7.5 | Followup for Adverse Events | 30 |
| 7.6 | Safety Monitoring | 30 |
| 8. | INTERVENTION DISCONTINUATION | 33 |
| 9. | STATISTICAL CONSIDERATIONS | 35 |
| 9.1 | General Design | 35 |
| 9.2 | Sample Size and Randomization | 36 |
| 9.3 | Definition of Populations..... | 37 |
| 9.4 | Interim Analyses and Stopping Rules..... | 37 |
| 9.5 | Outcomes | 37 |
| 9.6 | Data Analyses | 40 |
| 10. | DATA COLLECTION AND QUALITY ASSURANCE | 41 |
| 10.1 | Data Collection Forms..... | 41 |
| 10.2 | Data Management | 44 |
| 10.3 | Quality Assurance..... | 44 |
| 10.3.1 | Training..... | 44 |
| 10.3.2 | Quality Control Committee | 44 |
| 11. | PARTICIPANT RIGHTS AND CONFIDENTIALITY | 45 |
| 11.1 | Institutional Review Board (IRB) Review | 45 |
| 11.2 | Informed Consent Forms | 45 |
| 11.3 | Participant Confidentiality..... | 45 |
| 11.4 | Study Discontinuation | 46 |
| 12. | COMMITTEES | 46 |
| 13. | PUBLICATION OF RESEARCH FINDINGS..... | 46 |



| | |
|---|-----------|
| 15. SUPPLEMENTS/APPENDICES | 46 |
|---|-----------|

| | |
|-----------------------------|-----------|
| 14. REFERENCES | 47 |
|-----------------------------|-----------|

I. Procedures Schedule

II. Informed Consent Form Template

III. Other (add as many appendices as necessary)



STUDY TEAM ROSTER

Robyn Sysko
(212) 659-8724
robyn.sysko@mssm.edu

Tom Hildebrandt
212-659-8673
tom.hildebrandt@mssm.edu

Eve Freidl
(917) 414-9292
eve.freidl@mssm.edu

Kurt Schulz
(917) 273-8981
kurt.schulz@mssm.edu

Center of Excellence in Eating and Weight Disorders
Icahn School of Medicine at Mt. Sinai
One Gustave L. Levy Place, Box 1230
New York, NY 10029

PARTICIPATING STUDY SITES

Icahn School of Medicine at Mt. Sinai

PRÉCIS

Avoidant/restrictive food intake disorder is commonly associated with severe nutritional deficiencies, low weight/growth for age and sex, and significant distress, and can cause serious psychological and medical sequelae and functional impairment across the lifespan. The core feature of ARFID is a pervasive pattern of food avoidance, related to a lack of interest in eating or food, sensory characteristics of food, or concern about the aversive consequences of eating. Studies examining interventions for ARFID are limited, and additional options for intervention are needed. Mind-body interventions are well-matched to individuals with ARFID because of their physiologically driven aversion to food-cues, with interoceptive experiences overwhelming the rewarding (natural reinforcing) properties of food and reduce approach behavior. Our group recently developed and tested a brief 6-session mindfulness-based interoceptive exposure intervention for families of patients with anorexia nervosa and related conditions. The intervention focused on families supporting adolescents to reach a threshold of increased tolerance of the aversive emotion of disgust and greater engagement in approach behavior during feeding. Although food avoidance is a shared feature across conditions, adolescents with ARFID and those with other eating disorders are distinct populations. Our success with this prior mechanistic study provides a framework for the use of interoceptive



exposure. Given differences in the clinical presentations, this project will establish essential information about the feasibility and acceptability of a comprehensive mind and body family intervention for youth with ARFID; specifically a mindfulness-based interoceptive exposure (MBIE) for the high priority outcomes of health restoration and emotional well-being. A total of 57 adolescents with ARFID (aged 12-18) will be recruited to receive MBIE in an innovative dose-optimization approach to assess when a clinically-meaningful outcome is achieved, and assess tolerability and treatment characteristics, with the aim to distilling the most potent form of MBIE in 40 completers. We will: (1) explore the feasibility of recruitment, retention, and data collection procedures with youth with ARFID at end of treatment, (2) establish the acceptability and adherence of the MBIE intervention, and (3) evaluate the number of MBIE sessions required to observe changes in the number of foods avoided and mindfulness skills. These data can help to inform the utility of larger more definitive studies that have the potential to make a significant impact on the health and functioning of adolescents with ARFID.

This project aims to establish the feasibility and acceptability of a comprehensive mind and body intervention; specifically a mindfulness-based interoceptive exposure (MBIE) for families of youth diagnosed with avoidant/restrictive food intake disorder. As there are few psychological treatments available for these patients, the application would offer crucial data to determine whether this intervention could be examined in a mechanistic trial of complementary and integrative health approaches and/or a fully powered robust controlled trial of efficacy.

Study Title

Family-Based Interoceptive Exposure for Avoidant Restrictive Food Intake Disorder

Objectives

Primary Objective:

Explore patient tolerability with MBIE in youth with ARFID.

Secondary Objectives:

Explore the feasibility of recruitment, retention, adverse events, and data collection procedures with youth with ARFID during an MBIE intervention.

Establish the acceptability and adherence of the MBIE intervention.

Evaluate the number of MBIE sessions (dose response) required to achieve a clinically meaningful outcome and acceptable tolerability.

Design and Outcomes

In this single-site trial, we will use a phase I, non-randomizing, dose-optimizing (20 sessions) clinical trial design to examine feasibility and appropriate duration of treatment for a cohort of N=40 youth ages 12-18 with ARFID. Interview, self-report, anthropometrics, laboratory feeding, and behavioral task data will be used to



characterize the sample to their response to treatment over time.

Interventions and Duration

MBIE targets increasing psychological flexibility and acceptance by decreasing avoidance and attempts to control distressing or undesired internal experiences,¹ and includes psychoeducation, targeted mindfulness practice, in vivo exposures, and counter-conditioning. MBIE will be administered in 20 sessions. Follow-up assessments will be completed at session 5, 10, 15, and 20. The final assessment will take place 3 months after treatment ends. Total participation will last 9 months.

Sample Size and Population

The population in this study includes youth ages 12-18 with ARFID and at least one parent. We expect to consent 57 youth to achieve 40 completers (30% attrition).

1. STUDY OBJECTIVES

1.1 Primary Objective

The primary objective will explore patient tolerability with MBIE in youth with ARFID.

1.2 Secondary Objectives

A secondary objective will explore the feasibility of recruitment, retention, adverse events, and data collection procedures with youth with ARFID during an MBIE intervention.

A secondary objective will establish the acceptability and adherence of the MBIE intervention.

A secondary objective will evaluate the number of MBIE sessions (dose response) required to achieve a clinically meaningful outcome and acceptable tolerability.

| OBJECTIVES | ENDPOINTS | JUSTIFICATION FOR ENDPOINTS |
|---|--|---|
| Primary | | |
| Explore patient tolerability in youth with ARFID. | Patient tolerability will be assessed using the MBIE-adapted Therapy Suitability and Acceptability Scale between session 1 and session 20. | The RFA for this project intends to evaluate the feasibility, tolerability, acceptability and safety and preliminary effectiveness of approaches to improve mental health/functional outcomes |
| Secondary | | |



| OBJECTIVES | ENDPOINTS | JUSTIFICATION FOR ENDPOINTS |
|--|---|--|
| Explore the feasibility of an MBIE intervention in youth with ARFID. | <u>Recruitment</u> will be measured using total recruitment volume during the recruitment time period; <u>Retention</u> will be measured using rates of dropout between baseline and session 20; <u>Adverse events</u> will be measured using rates of adverse events between baseline and session 20; <u>Data collection procedures</u> will be measured using participant ratings of acceptability of assessments for total time and frequency | As above, feasibility is a primary focus of this RFA |
| Establish the acceptability and adherence of the MBIE intervention. | Adherence of the MBIE intervention will be measured with ratings of therapy tapes of 20 sessions. MBIE-adapted Therapy Suitability and Acceptability Scale will measure MBIE intervention over the course of 20 sessions. | As above, acceptability is a primary focus of this RFA |
| Evaluate the number of MBIE sessions (dose response) required to achieve a clinically meaningful outcome and acceptable tolerability | Evaluate the number of MBIE sessions required to achieve a clinically meaningful outcome and acceptable tolerability using Function Food Hierarchy and Function Food Avoidance | As above, preliminary effectiveness is a primary focus of this RFA |

2. BACKGROUND AND RATIONALE

2.1 Background on Condition, Disease, or Other Primary Study Focus

As ARFID was first included as a formal diagnosis in the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders,² data are limited, but indicate the condition is a significant public health concern. Overall prevalence is estimated at 3% of the population,^{3, 4} with ARFID more commonly found in specialty care settings (7%-



23%).⁵⁻⁸ Patients may develop ARFID secondary to medical problems producing gastrointestinal dysfunction or pain,^{9, 10} and are at increased risk for serious medical sequelae secondary to malnutrition,⁵ including amenorrhea,¹¹ bradycardia, prolonged QT interval, and electrolyte abnormalities like hypokalemia.¹² Individuals with ARFID experience marked impairments in physical and mental health-related quality of life and role performance,¹³ and co-occurring psychiatric conditions occur frequently, including anxiety disorders (e.g., 50% with generalized anxiety disorder^{5, 14} autism spectrum disorder,⁷ and attention deficit hyperactivity disorder.⁷ Consequently, patients with ARFID are complex and risky populations to manage clinically.

At this time, there are no randomized controlled trials evaluating the efficacy of outpatient treatment for ARFID in adolescents or adults. In day treatment or inpatient units, children with ARFID may be provided with more intensive interventions that often require medical supervision, such as oral nutritional formula supplements or tube feeding.¹⁵ Enteral feeding allows patients to avoid the sensory experience of food or the threat of choking, which could inadvertently perpetuate symptoms, and further, day treatment and inpatient programs can be effective,¹⁶ but are costly, difficult to scale, and most appropriate for severely ill children and adolescents. Uncontrolled data suggest that family-based therapy (FBT) is a promising treatment for younger patients with this condition.¹⁷ FBT is unique in its atheoretical approach to the etiology of disordered eating, and does not hypothesize any model for the maintenance of the pathological food avoidance observed by patients with ARFID. However, it does (a) empower the parents to take control of food decisions, and (b) separate the child from the avoidance behaviors to reduce frustration and negative food environments.

Interoceptive exposure (IE) interventions aim to target sensitivity or vigilance to visceral sensations and are used for a range of conditions, including panic disorder¹⁸⁻²¹ and irritable bowel syndrome.^{22, 23} The target of treatment is associative learning between a conditioned fear of internal cues and fear, distress, or harm producing avoidance and maintaining catastrophic beliefs.²⁴ IE typically involves repeated exposure to feared internal bodily sensations, identification of maladaptive cognitions elicited by these sensations, and practice tolerating these sensations without avoidance or distraction. The goal is to extinguish the conditioned fear response by repeatedly inducing and enduring these uncomfortable body sensations.²⁰ Similar to fear-based models of exposure, the assumption is that exposure will activate inhibitory learning to suppress the aversive expectancy and allow for natural approach behaviors to resume. An alternative model of IE, developed by our group, assumes that inhibitory learning may not be primary to this form of exposure. Rather than reduce expectancy of harm, which will only occur when an exposure does not yield a reflexive aversive response, and as described in detail below, our approach uses mindfulness-based interventions with IE to increase tolerance of the aversive emotion (without expectancy that it will change) and applies counter-conditioning to alter the valence of the conditioned stimulus, resulting in a greater reflexive response to approach food.

This protocol includes a feasibility study using our experience applying IE in LWEDs to develop a related and expanded intervention for ARFID. The intervention



incorporates mindfulness skills and practice with exposures addressing our physiological model of disgust to enhance food-cue extinction and decrease food avoidance. Consequently, this mind-body intervention targets a unique aspect of the physical feedback between gut and brain characterized by parasympathetic response to feeding threats.

2.2 Study Rationale

Avoidant/restrictive food intake disorder is commonly associated with severe nutritional deficiencies, low weight/growth for age and sex, and significant distress, and can cause serious psychological and medical sequelae and functional impairment across the lifespan.^{2-4, 20} The core feature of ARFID is a pervasive pattern of food avoidance, related to a lack of interest in eating or food, sensory characteristics of food, or concern about the aversive consequences of eating.^{2, 20} Studies examining interventions for ARFID are limited,^{22, 25} and additional options for intervention are needed. Mind-body interventions are well-matched to individuals with ARFID because of their physiologically driven aversion to food-cues, with interoceptive experiences overwhelming the rewarding (natural reinforcing) properties of food and reduce approach behavior.^{23, 24, 26, 27} Our group recently developed and tested a brief 6-session mindfulness-based interoceptive exposure intervention (MH109639; PI: Hildebrandt) for families of patients with anorexia nervosa and related conditions. The intervention focused on families supporting adolescents to reach a threshold of increased tolerance of the aversive emotion of disgust and greater engagement in approach behavior during feeding. Although food avoidance is a shared feature across conditions, children with ARFID and adolescents with eating disorders are distinct populations. Our success with this prior mechanistic study provides a framework for the use of interoceptive exposure.^{28, 29}

Given differences in the clinical presentations, this project will establish essential information about the feasibility and acceptability of a comprehensive mind and body family intervention for youth with ARFID; specifically a mindfulness-based interoceptive exposure (MBIE) for the high priority outcomes of health restoration and emotional well-being. A total of 40 children with ARFID (aged 12-18) will be recruited to receive MBIE in an innovative dose-optimization approach to assess when a clinically-meaningful outcome is achieved, and assess tolerability and treatment characteristics, with the aim to distilling the most potent form of MBIE. We expect to consent 57 youth to achieve a final sample of 40 completers. We will: (1) explore the feasibility of recruitment, retention, and data collection procedures with youth with ARFID at end of treatment, (2) establish the acceptability and adherence of the MBIE intervention, and (3) evaluate the number of MBIE sessions required to reach a clinically meaningful outcome. These data can help to inform the utility of larger more definitive studies that have the potential to make a significant impact on the health and functioning of children with ARFID.

3. STUDY DESIGN

The core feature of ARFID is a pervasive pattern of food avoidance, related to a lack



of interest in eating or food, sensory characteristics of food, or concern about the aversive consequences of eating, resulting in severe nutritional deficiencies, low weight/growth for age and sex, and significant distress.^{2, 20} Interoceptive exposure has been used in the treatment of low-weight eating disorders (LWEDs), with the goal is to extinguish the conditioned fear response associated with food by repeatedly inducing and enduring these uncomfortable body sensations.^{17, 20} Similar to fear-based models of exposure, the assumption is that exposure will activate inhibitory learning to suppress the aversive expectancy and allow for natural approach behaviors to resume. This protocol includes a feasibility study using our experience applying IE in LWEDs to develop a related and expanded intervention for ARFID. The Mindfulness-Based Interoceptive Exposure (MBIE) intervention incorporates mindfulness skills and practice with exposures addressing our physiological model of disgust to enhance food-cue extinction and decrease food avoidance. Consequently, this mind-body intervention targets a unique aspect of the physical feedback between gut and brain characterized by parasympathetic response to feeding threats.

In this single-site, non-randomized, trial at the Icahn School of Medicine at Mount Sinai, we will use a phase I, non-randomizing, dose-optimizing (20 sessions) clinical trial design to examine feasibility and appropriate duration of treatment for a cohort of N=57 youth ages 12-18 with ARFID. Interview, self-report, anthropometrics, laboratory feeding, and behavioral task data will be used to characterize the sample to their response to treatment over time. Participants will receive 20 sessions of Mindfulness-Based Interoceptive Exposure. Follow-up assessments will be completed at sessions 5, 10, 15, and 20 and 3-months post intervention. Total participation will last 9 months.

Enrollment is expected to start in month 4, end in month 28, and assessments will end in month 33. The study will take approximately 3 years to complete.

Primary Objective:

Explore patient tolerability with MBIE in youth with ARFID.

Secondary Objectives:

Explore the feasibility of recruitment, retention, adverse events, and data collection procedures with youth with ARFID during an MBIE intervention.

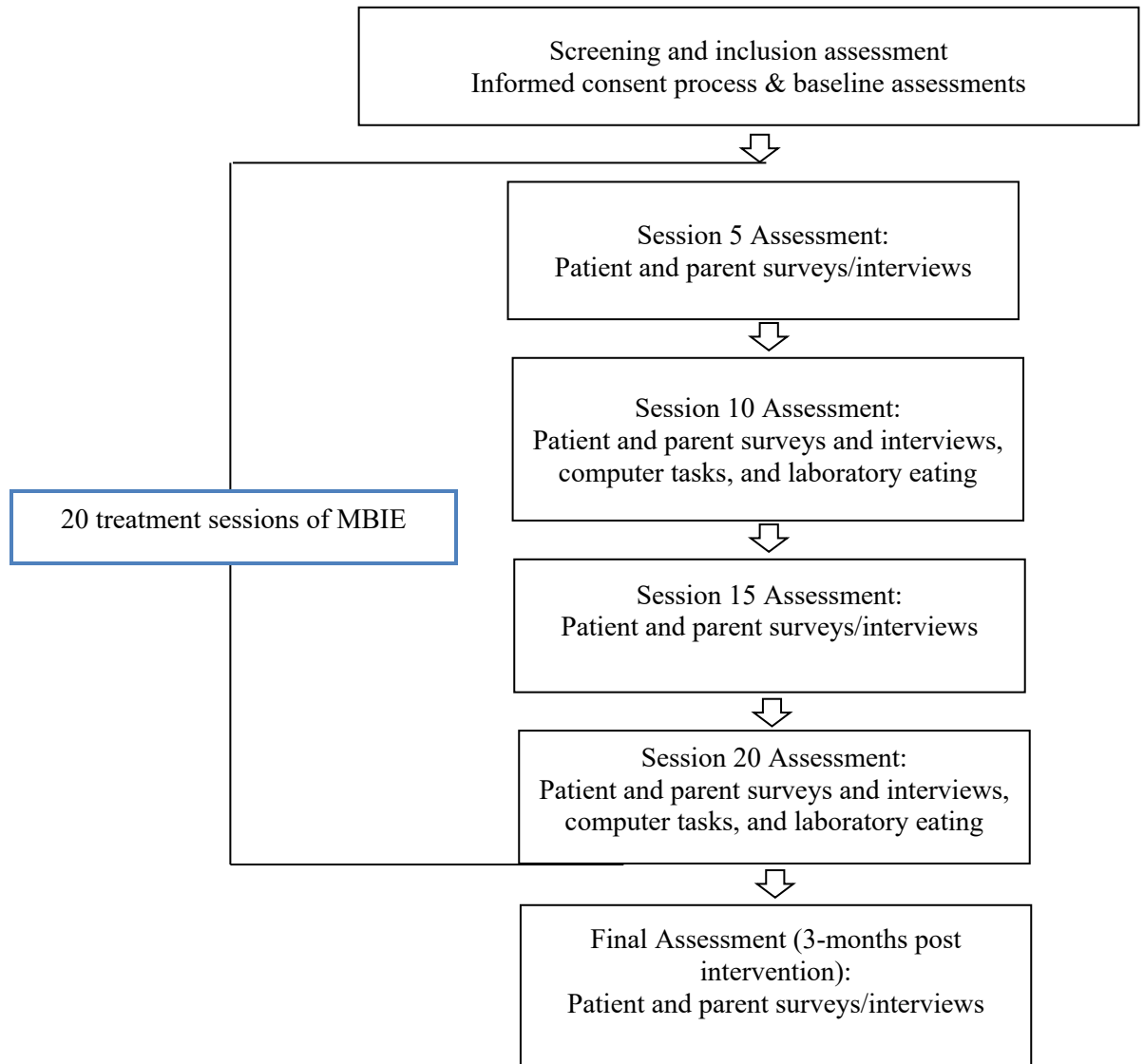
Establish the acceptability and adherence of the MBIE intervention.

Evaluate the number of MBIE sessions (dose response) required to achieve a clinically meaningful outcome and acceptable tolerability.

Many psychological treatments for eating disorders yield an early response^{30, 31} in the first few weeks of treatment. It is therefore reasonable to expect a similar pattern with ARFID, which would suggest value in a short-term intervention. We have chosen to apply an innovative dose-optimization approach, a design most commonly utilized with pharmacologic treatments, to determine how many sessions are needed to reach



a clinically meaningful outcome (i.e., tolerate consuming a food rated as $\geq 70/100$ subjective units of distress in natural environment). Within a restricted number of sessions (20), a dose optimizing design will establish optimal parameters, including: (1) the empirically derived ideal number of sessions and (2) targets for within-session decisions about escalating exposure on the Food Hierarchy.



4. SELECTION AND ENROLLMENT OF PARTICIPANTS

Will recruit, consent, & enroll N=57 for a final completers of N=40 (allowing for 30% drop-out/screen failure rate).4.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria, which is assessed during the screening phase:

Patient:



- Aged 12-18
- Speaks English
- Permission from pediatrician or equivalent to receive outpatient care, including that the patient does not meet criteria for hospitalization based on the American Psychiatric Association guidelines
- Diagnosis of Avoidant Restrictive Food Intake Disorder, as assessed by the EDA-5

Parent:

- Has a child aged 12-18 with a diagnosis of ARFID
- Speaks English

4.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

- Comorbid psychotic or bipolar disorder
- Psychiatric medication initiated or with a dosage change in the two weeks prior to baseline testing
- Active suicidal ideation
- Major medical condition (e.g., diabetes mellitus, pregnancy)
- Current substance dependence, as evidenced by tolerance and withdrawal
- Evidence of anatomical findings by imaging (e.g., swallow study) that would prevent safe consumption of the shake or those with a percutaneous endoscopic gastrostomy or other similar feeding tube insertion
- We will plan to exclude children with visual or physical limitations that would preclude watching a screen and using a finger to respond with mouse clicks (e.g., blindness, epilepsy if exposure to flashing lights at certain intensities or to certain visual patterns can trigger seizures).
- A patient or parent unwilling to participate in the study

4.3 Study Enrollment Procedures

Recruitment Plan and Location:

The Principal Investigator and study team at Mount Sinai has extensive experience recruiting children and adolescents for research studies over the last decade. In each of the last several years, the EWDP provided services to more than 500 unique individuals. Our records indicate approximately 50 per year would have met criteria for inclusion of this protocol. In addition, the Center of Excellence in Eating and Weight Disorders includes a continuum of outpatient care focused on children and adolescents with eating disorders in an area (NYC) with high population density. Drs. Sysko and Hildebrandt will use existing contacts from clinical, administrative, and teaching responsibilities at the Mount Sinai Health System, including referring providers in Pediatrics, to ensure that recruitment of patients with ARFID is more than sufficient to complete the project.

Participants will be recruited from the Center of Excellence for Eating and Weight



Disorders (EWDP) at the Icahn School of Medicine at Mount Sinai (MSSM), the Mount Sinai System, flyers in the community at stores and businesses that have provided permission, and online platforms. As part of ongoing community outreach efforts, Drs. Sysko, Hildebrandt, and other staff present at secondary schools in the area to student and parent groups, and consult with school counselors about adolescents who require additional services. Anyone booked for a consent visit will be email a consent form to review prior to the visit to allow for additional time to consider participation.

EWDP: Participants will be recruited through typical referral pathways for the Eating and Weight Disorders Program (EWDP). New patients most commonly call after finding the clinic through our website or speaking with another provider/center. EWDP staff will speak with new patients or current patients to introduce the study briefly and ask if the participant is interested in hearing more. If so, they will be scheduled for a visit to review consent and provide screening information.

Mount Sinai Media System: We will advertise using Mount Sinai's broadcast email system and the Mount Sinai media center. Approved text will be distributed to employees via a broadcast email and will include the study team's contact information. Approved text will be used by the media center and displayed in offices and on computers throughout the Mount Sinai campuses. Potential subjects can use the contact information displayed on these advertisements to contact our team for more information regarding the research study.

Community Flyers: We will advertise our study by displaying IRB approved flyers with a brief description of the study and our research team's contact information throughout the community. Interested participants can contact the research team by using the information on the flyer to call the EWDP and ask for the researcher listed on the flyer. Some flyers will have QR codes. These codes will be used to automatically direct the participant to our study staff or to additional study information. Each flyer will include 2 QR codes: one code will trigger an email to automatically populate on their device that the individual can use to send an inquiry directly to us; the second QR code will be used to direct individuals to a REDCap database. This database will allow us to share more details about the study and then, if interested, they may enter their name and email for us to reach out to them. The study description used will match the approved Recruitment Script. This database is separate from the study data and only used to facilitate reaching out to new participants expressing interest in our study. No information will be stored in this database related to inclusion, exclusion, eligibility status, or study data.

Online Platforms: We will advertise our study online using platforms such as Facebook, Instagram (owned by Facebook), ResearchMatch, Craigslist, Reddit, and professional conference platforms. Study advertisements distributed online, comprising of IRB approved text and flyers, will include the study team's contact information that potential subjects might use to request additional information from the research team.



Some flyers will have QR codes. These codes will be used to automatically direct the participant to our study staff or to additional study information. Each flyer will include 2 QR codes. One code will trigger an email to automatically populate on their device that the individual can use to send an inquiry directly to us. A 2nd QR code will be used to direct individuals to a REDCap database. This database will allow us to share more details about the study and then, if interested, they may enter their name and email for us to reach out to them. The study description used will match the approved Recruitment Script. This database is separate from the study data and only used to facilitate reaching out to new participants expressing interest in our study. No information will be stored in this database related to inclusion, exclusion, eligibility status, or study data.

Diversity Recruitment Efforts:

As our program is located in a major metropolitan center, we anticipate a similar distribution to our recent trial of adolescents with low weight eating disorders. In that study, a total of 20% of adolescents described themselves as Hispanic/Latino, with additional designations for race reported as white (70%), mixed race (21%), Black or African American (4%), and Asian (4%). We will make special efforts to recruit participants from the racially and ethnically diverse areas immediately surrounding the Icahn School of Medicine at Mount Sinai, including referrals from the community-based Adolescent Health Center, and the greater New York metropolitan area. In our recruitment, we will utilize existing networks of clinicians in the metropolitan area and community service announcements. Our planned enrollment table reflects the ethnic composition of extant data, our prior studies, and the community surrounding Mount Sinai.

Vulnerable Participants:

Children ages 12-18 will be the focus of this study, as adolescence is a critical period of development when individuals with avoidant/restrictive food intake disorder are most likely to present for treatment. At this time, there are no empirically supported treatments for individuals with avoidant/restrictive food intake disorder. Given the extant data, inclusion of children offers the best opportunity for pertinent research to inform science.

Documentation:

Eligibility status and reasons for ineligibility will be stored for all participants in a screening log.

Screen Failures:

Screen failures are defined as participants who consent to participate in this study, but do not meet the criteria for participation in this study because of meeting one or more



exclusions criteria or for not completing all screening procedures. Formal withdrawal or failure to complete scheduled measures will constitute drop-out for the study rather than a screen failure. Any participant who drops or is a screen failure may continue to seek treatment in the EWDP.

5. STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

Once eligibility is determined, baseline procedures have been completed, participants will complete 20 sessions over 24 weeks. At least one parent/legal guardian will need to attend all therapy sessions. Parents will be asked to attend (in person or remote) as much of the session as possible, as the intervention is family-based, and adolescents typically have limited control over the food environment in their home. Further, given the model on which the treatment is based, adolescents with ARFID avoid food as a result of fear, worry, or disgust. We would not expect there to be an independent approach of these stimuli outside of session without parental assistance prior to the lessening of fear, worry, or disgust associated with food. In two-parent households, parents often have different levels of responsibility for feeding. Therefore, we will ask the parent who can take primary responsibility for the preparation and provision of meals during treatment to attend sessions to assist with implementation of exposures at home. Weight and height is measured at each session. Participants will complete the Functional Food Hierarchy and Functional Food Avoidance Scale at each of the 20 MBIE sessions. Parents will also provide a rating of weekly progress with food avoidance in each of the 20 MBIE sessions.

MBIE will be administered by a trained clinician for 20 sessions. The intervention will be delivered through the Eating and Weight Disorders Program at the Icahn School of Medicine.

As in other mindfulness based treatments, including for eating pathology,³²⁻³⁷ MBIE targets increasing psychological flexibility and acceptance by decreasing avoidance and attempts to control distressing or undesired internal experiences,¹ and includes psychoeducation, targeted mindfulness practice, in vivo exposures, and counter-conditioning.

Session I. The first session focuses on psychoeducation about types of anxiety (fear, worry, disgust),^{38, 39} ways that a lack of non-judgmental body awareness can contribute to interoceptive deficits, and eliciting information on symptoms and functional impairments related to food avoidance. The child's language for distress related to feeding (e.g., "I just don't like it," "Makes me feel gross", etc.) is utilized, and specific attention is given to the somatic experiences associated with past and present aversive/avoided foods. The therapist elicits examples of each type of emotion and has the family complete an assessment of broad anxiety domains, which is used as the rationale for targeting disgust for overcoming food avoidance. The family, in conjunction with therapist, develop a "Functional Food Hierarchy" which



allows for ranking of foods/eating elements (e.g., food amount, preparation, etc.) on the basis of difficulty (subjective units of distress) and function (useful in the child's day-to-day life, eating pizza at birthday party, restaurant food with friends, etc.). Planning for homework also occurs (i.e., completing the hierarchy, deciding a food to use in the next session).

As a conceptual framework for the clinician, the treatment is divided into phases (as below), to guide the structure and content of the exposures; however, all sessions are focused on exposures along the continuum of the food hierarchy.

Phase I. Phase I (sessions 2-9) includes interoceptive exposures as behavioral experiments of eating foods that elicit disgust and learning to tolerate the experience (e.g., it is normal to have difficulty eating when you feel disgusted and you can learn to eat anyway) using two primary approaches: counter conditioning and mindfulness practice.

For counter conditioning, the therapist orients families to the goal of disrupting the learned association between visceral cues of eating and negative emotions. A list of activities is generated for use during exposures to help pair eating and positive experiences, which is reinforced by daily exposure practice and counter-conditioning as homework (e.g., re-label stomach discomfort as “like the big drop of the roller coaster”).

Mindfulness practice is modeled during interoceptive exposures. Based on our prior experience and the mindfulness literature,⁴⁰⁻⁴³ MBIE focuses on: 1) observing, 2) describing, 3) acting with awareness, 4) nonjudging of inner experience, and 5) non-reactivity to inner experience. To address each of these five facets, sessions include practice being in the present moment and utilizing non-judgmental language to describe eating and the physical sensations of disgust. Judgmental language can enhance feelings of disgust, making eating more difficult to tolerate, increasing the desire to avoid eating, or leading to actions designed to escape eating. Parents use firm empathy to support their children in continuing to engage with both the exposure (e.g., taking bites of food), observing physical sensations (e.g., throat feeling like it is closing, heart racing) and nonjudgmental description when disgust increases during the session. Practice occurs over multiple sessions. Additional practice includes the Raisin Exercise (with a raisin or similar food item) for present-moment awareness of the five senses, families engaging in a breath control exercise alternating observing typical breathing and paced breathing to illustrate the paradoxical effect of attempts to control feeding (i.e., requires substantial effort and increases negative affect around eating). Families are introduced to willing discomfort, and the idea of experiencing discomfort as a necessary part of life because in trying to avoid or diminish discomfort, rather than accepting it, this usually leads to suffering. The final mindfulness exercise in Phase I is body scanning, or attending to parts of the body and bodily sensations in a gradual sequence from feet to head to bring awareness to every single part of the body, rather than focusing only on feeding related sensations.



Phase II: Phase II (sessions 11-20) extends the work of Phase I by increasing the complexity and contextual cues associated with exposures. For example, instead of eliciting disgust to pizza alone, varied specific contexts for exposure (e.g., time of day, type of clothing, exposure immediately after a meal) and predictability (e.g., parents choose randomly from hierarchy) are used to decrease the ability of the child to prepare for exposures. An additional focus of this phase is on refining counter conditioning (e.g., identifying the most effective strategies) and developing mastery of mindfulness strategies. Practice during this phase will include mindful listening (e.g., comparing and contrasting mindful negative versus positive thoughts), self-compassion (e.g., purposeful kindness during a food exposure), and additional use of skills from Phase I that were designated as most useful for tolerating distress. By expanding comfort with mindfulness practice, participants can utilize skills beyond tolerating exposures to other health related effects and the management of stress overall.

End of Phase II: At session 20, families will assess progress, obstacles, and solutions. They will develop a maintenance plan to continue working on expanding food agency, mindful awareness and action, and functionality and consider how to handle regression (i.e., return of avoidance behavior).

Dosing:

In the 20 sessions of MBIE, an escalation of the ‘hierarchy dose’ will be determined by the dose-optimization algorithm whereby clinicians will ‘titrate’ exposure upwards until achieving a maximum tolerated dose (i.e., level on functional exposure hierarchy that patient initiates without withdrawal). As the Functional Food Hierarchy is scaled 0-100, this maximum dose would therefore be defined as reaching any item rated 100 without withdrawal. If this dose is reached prior to session 20, any additional sessions will focus on exposures to other items rated as 100. The first session is 90 minutes and the remainder 60 minutes. Families will be seen once weekly.

Risks:

There is the potential for participants to become upset, tired, anxious, or uncomfortable during visits during the study procedures or interviews. Participants may also experience fatigue when completing the tasks in the assessments. All evaluations will be conducted by trained clinicians and staff. If a participant becomes upset or anxious, a member of the study team will ask the patient if he/she/they wish(es) to continue their participation. The protocol will be discontinued if a participant experiences a level of emotional discomfort such that he/she/they wish(es) to end her participation in the protocol. He/she/they may end participation in this study at any time, with no consequence to the ability to access services at Mount Sinai in the future. If the participant experiences emotional discomfort as a result of participation in the study, the research team member administering the protocol will attempt to provide comfort to the participant, will contact the Principal Investigator, and will discuss with the participant the need for a referral for further mental health



services. To minimize fatigue, if the participant states feeling tired during testing or if the examiner notices this, the participant will be encouraged to take a break. Participants and parent(s) can defer scheduling of appointments to evaluate willingness to participate and subsequently resume treatment.

In the case of active suicidal or homicidal plans or intent revealed during the course of evaluation, a member of the clinical staff will evaluate the patient. If necessary, the participant will be taken to the emergency room or referred to an inpatient facility. If safety is compromised or could potentially be compromised by the discovery of a previously unknown psychiatric disorder during evaluation, the procedure above will be followed. If not (e.g., the discovery of a Major Depressive Disorder with no psychotic features and no suicidality), the participant and parents will be notified and encouraged to seek help at the time the condition is identified. In the case of abuse or neglect, this would be reported in accordance with state laws. The patient's primary pediatrician will also be notified assuming a written release is signed by the participant (if 18) or their parent during enrollment.

As in any research including PII or PHI, there is a risk of loss of confidentiality due to unauthorized access to study records or disclosure without the participant's permission. We try to avoid this by storing study data separately from PII and PHI and utilizing multiple steps of permissions to access data including required employee clearance, ISMMS log-in for access to study drives, password protection, and database level permissions managed by the project manager.

Group Risks – In the process of sharing data, although name will not be given to other researchers, basic information such as race, ethnic group, and sex may be shared. It is possible that such findings could be used to support harmful stereotypes or discrimination.

Benefits:

Potential benefits to the patients in this proposed study includes an evaluation at no cost, and the possibility of a reduction of symptoms associated with low weight eating disorders. Indirect benefits include benefits to future patients, researchers, clinicians, and health care planners could include valuable information about ways to improve outcomes in adolescents with low weight eating disorders. Evaluating effective interventions in the treatment of adolescent low weight eating disorders and prevention strategies is of the utmost importance in order to improve the outcome in this disorder.

Assessment of Potential Risks and Benefits:

The risks are a minor increase over minimal risk but no direct benefit.

5.2 Handling of Study Interventions

All sessions will be videotaped. Therapists will be a clinical psychologist or advanced



post-doctoral fellow and experienced with delivering treatment for ARFID. Study therapists will be trained in MBIE by Dr. Hildebrandt (Co-I), who developed the manual utilized previously in our program, prior to providing this treatment. During the study, the PI will lead weekly 1-hour supervision meetings with therapists, including role plays and viewing videotaped sessions, to ensure treatment integrity. All tapes will be coded for adherence using checklists developed during our prior trial using published methods.^{30, 32, 44, 45}

5.3 Concomitant Interventions

5.3.1 Allowed Interventions

N/A

5.3.2 Required Interventions

N/A

5.3.3 Prohibited Interventions

N/A. As this intervention has not yet been tested, and its effects are not known, other treatment (research or clinical) will not be prohibited. Concurrent treatment will be assessed at baseline and in each session to inform statistical analyses.

5.4 Adherence Assessment

All treatment sessions will be video recorded to be coded to ensure therapist adherence to treatment protocol. Adapting forms and procedures from previous studies, we will train masters or doctoral level psychologists to rate all sessions. The Therapy Integrity scales^{13, 17} will measure elements of MBIE (process, common factors that occur every session, interventions specific to each session), therapist competence, therapist differentiation (i.e., inclusion of non-treatment elements), and adherence. Each item is rated on a Likert scale on extent of use of the treatment element, and a scale on the quality of delivery of the intervention. Therapists and external raters will complete a checklist of activities addressed in each session, and the Working Alliance Inventory.⁴⁶ Two raters will double-code 20% of the sessions for ICCs to determine checklists can be reliably rated for each session.

6. STUDY PROCEDURES

6.1 Schedule of Evaluations

| Week* | 0 | 5 | 10 | 15 | 20 | 36 |
|------------------|----------------------|-----------|------------|------------|------------|------------------|
| Procedures | Baseline / Screening | Session 5 | Session 10 | Session 15 | Session 20 | Final Assessment |
| Informed Consent | X | - | - | - | - | - |
| Demographics | X | - | - | - | - | - |



| | | | | | | |
|---|-------|---|------|--------|---------------------|------------------|
| Medical History | X | - | - | - | - | - |
| Eligibility Assessment | X | - | - | - | - | - |
| EDA-5 | X | - | - | - | - | - |
| C-SSRS | X | - | - | - | - | - |
| Therapy Suitability/Acceptability, Assessment Acceptability | X | X | X | X | X | X |
| Height / Weight | X | Measured weekly in sessions 1-20 and at each assessment | | | | |
| SFQ-ARFID Scale | X | X | X | X | X | X |
| SFQ-PHP Scale | X | X | X | X | X | X |
| PvARFID | X | X | X | X | X | X |
| CAMM | X | X | X | - | X | X |
| BAQ | X | X | X | - | X | X |
| DSQ | X | X | X | - | X | X |
| Extinction Learning | X | - | - | - | - | - |
| Disgust Bias (Go/No-go) | X | - | - | - | - | - |
| Single Item Meal/VAS pre-and post | X | - | X | - | X | - |
| Fidelity | - | Measured weekly in sessions 1-20 | | | | |
| SubtypeCAS VAS | - | Measured at session 1 | | | | |
| Functional Food Hierarchy | - | Measured at sessions 2, 10, 19 | | | | |
| Functional Food Avoidance | - | Measured weekly in sessions 2-19 | | | | |
| Total Participant Time: | 2 hrs | 10 min | 1 hr | 10 min | 1 hr | 20 min |
| | | | | | Total Hours: | Approx 25 |

6.2 Description of Evaluations

6.2.1 Screening Evaluation

Consenting Procedure

Informed consent will be conducted by a trained clinical or research study staff member who will review the study protocol and obtain voluntary written informed consent, on paper or using the full-study e-consent form, prior to completing study procedures in accordance with the PPHS of Mount Sinai. Our consent documents will be submitted with the protocol.

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and their parents. Written documentation of informed consent is required prior to starting intervention/administering study intervention. The consent forms will include an explanation of study procedures, time commitments, risks and benefits, alternatives to participation, confidentiality information, and the rights or research subjects. The following consent materials are submitted with this protocol: Parental Permission, Main ICF, and Main ICF for parent.



- For children 12-17: The Parental Permission form is used for obtaining parental consent for their child to participate as well as indicating their own consent to participate. This form also documents assent. The Main ICF will be used if a child turns 18 after consenting, but prior to completing the study.
- For 18 year olds: The Main ICF will be used for consenting the patient and the Main ICF for parent will be used for the parent to document their own participation.

No reference to the potential subject's identity will be made outside of closed quarters. All study related questions from study participants that a research staff member is unable to address will be referred to the Principal Investigator or other Co-Investigators.

Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. Anyone booked for a consent visit will be emailed a consent form to review prior to the visit to allow for additional time to consider participation. During the consent visit, study staff will explain the research study. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants.

Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants will have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. Participants may take the consent form home with them before beginning the baseline assessments to further consider the procedures.

The participant will sign the informed consent document prior to any procedures being done for the study. The consent form will explicitly notify participants that participation is voluntary, can be discontinued at any time and will not affect their medical care or status in the Mount Sinai Health System. A copy of the informed consent document will be given to the participants for their records.

For in-person consent: Consent/assent will include the investigator or another member of the research staff explaining the protocol, and if the patient is interested in participating, this clinician will certify in writing that the participant indeed understands the protocol and signs a formal consent document and will be provided with a copy of the signed consent form document.

For virtual visits: A member of the study staff will review the study protocol and obtain written consent using the full-study e-consent form in REDCap over a HIPAA compliant video platform (e.g., Zoom). The potential subject will provide their e-signature and name as well as the date of consenting process on the e-consent form while on Zoom with the staff member. After the subject submits the form, the study staff member obtaining the consent will provide their signature, name, and the



consenting date on the signed e-consent form and send a copy of the form to the participant via an encrypted email.

6.2.2 Enrollment, Baseline, and/or Randomization

The first baseline visit, lasting approximately 2 hours, will include consent and screening procedures with both the patient and parents to determine eligibility. This visit includes a physical exam, interview questions to determine inclusion/exclusion criteria, online surveys, single item meal, extinction learning task, and go/no-go task.

1. The physical exam, conducted by Eve Friedl, MD will include measurements of height and weight.
2. Interview questions will assess the inclusion/exclusionary questions and presence of an eating disorder. This assessment includes the Eating Disorder Assessment (EDA-5)²⁹ and Columbia Suicide Rating Scale (C-SSRS).³¹
3. Online REDCap questionnaires will be completed by the patients and parents.
 - Parents will complete the Stanford Feeding Questionnaire ARFID (SFQ-ARFID)³⁵ and Stanford Feeding Questionnaire Parental Feeding Problems scales (SFQ-PFP),³⁵ and the Parents versus ARFID scale (PvARFID).³⁶
 - Patients will complete the Child and Adolescent Mindfulness Measure (CAMM),^{37, 47} Body Awareness Questionnaire (BAQ),^{39, 43} and the Dietary Screener Questionnaire (DSQ).^{43, 48}
4. Single-Item Meal:
Participants will be given a strawberry yogurt shake in a large container. The shake will replace a typical scheduled meal for that day (i.e., breakfast, lunch, dinner). The nutritional composition of the shake is similar to that of standard nutritional supplements, like Ensure or Boost. Visual analog scales (VASs) for liking, desire to eat, hunger, fullness, sweetness, saltiness, and loss of control will be completed pre- and post-meal. This procedure will take approximately 15-30 minutes.
5. Extinction Learning Task (15 Minutes):
The task is a computer task that tests associations between food and level of disgust. Pictures of food are shown including fresh and rotten versions of each and participants then rate on a scale from yucky to yummy for each.
6. Go/No-go task (20 minutes):⁴²
This task measures the effect of emotion on the ability to inhibit responses to rare non-targets (no-go trials) in the context of responding to frequent targets (go trials). Participants respond to an instructed go signal (i.e., happy faces) of faces portraying different types of emotion (happy, neutral, disgust) flashing on the screen. After each trial, participants will be re-instructed to respond to a different (or the same) go signal (i.e., happy faces).

To evaluate eligibility for receiving outpatient treatment as part of this protocol, participants will need to be evaluated and designated as appropriate to receive outpatient therapy by their pediatrician/primary care doctor. After consent/assent is



completed, the RA will collect the participant's PCP contact information and fax the PCP a clearance letter explaining the study and what is needed for the participation. Enrollment will not be initiated prior to receiving information from the primary treating clinician that will be reviewed by the medical director, Dr. Freidl.

Randomization

N/A

6.2.4 Follow-up Visits

Follow-up assessments are conducted during the following timepoints: after session 5, session 10, session 15, and session 20. Each assessments includes different procedures. The procedures for Single Item Meal, Extinction Learning task, and Go/No-Go task will be conducted as described in the baseline section.

- **Session 5 Follow-Up Assessment**

This assessment includes REDCap surveys for both the participant and parent and will take 10 minutes to complete.

REDCap Surveys:

The online surveys for this assessment will be emailed to the participant and parent to be completed over the course of 1 week.

- Parents will complete: Stanford Feeding Questionnaire ARFID (SFQ-ARFID),³⁵ Stanford Feeding Questionnaire Parental Feeding Problems scales (SFQ-PFP),³⁵ and Parents versus ARFID scale (PvARFID).³⁶
- Patients will complete: Child and Adolescent Mindfulness Measure (CAMP),^{37, 47} Body Awareness Questionnaire (BAQ),^{39, 43} Dietary Screener Questionnaire (DSQ),^{43, 48} Therapy Suitability and Acceptability Scale,¹⁷ and Assessment Acceptability Scale.

- **Session 10 Follow-Up Assessment**

This assessment includes the Single Item Meal and will last approximately 1 hour. Additionally, surveys for both the participant and parent will be administered.

REDCap Surveys:

The online surveys for this assessment will be emailed to the participant and parent to be completed over the course of 1 week.

- Parents will complete: Stanford Feeding Questionnaire ARFID (SFQ-ARFID),³⁵ Stanford Feeding Questionnaire Parental Feeding Problems scales (SFQ-PFP),³⁵ and Parents versus ARFID scale (PvARFID).³⁶



- Patients will complete: Child and Adolescent Mindfulness Measure (CAMM),^{37, 47} Body Awareness Questionnaire (BAQ),^{39, 43} Dietary Screener Questionnaire (DSQ),^{43, 48} Therapy Suitability and Acceptability Scale,¹⁷ and Assessment Acceptability Scale.

- Session 15 Follow-Up Assessment

This assessment includes surveys only and will take approximately 10 minute to complete.

REDCap Surveys:

The online surveys for this assessment will be emailed to the participant and parent to be completed over the course of 1 week.

- Parents will complete: Stanford Feeding Questionnaire ARFID (SFQ-ARFID),³⁵ Stanford Feeding Questionnaire Parental Feeding Problems scales (SFQ-PFP),³⁵ and Parents versus ARFID scale (PvARFID).³⁶
- Patients will complete: Therapy Suitability and Acceptability Scale.¹⁷

- Session 20 Follow-Up Assessment

This assessment includes the Single Item Meal and will last approximately 1 hour. Additionally, surveys for both the participant and parent will be administered.

REDCap Surveys:

The online surveys for this assessment will be emailed to the participant and parent to be completed over the course of 1 week.

- Parents will complete: Stanford Feeding Questionnaire ARFID (SFQ-ARFID),³⁵ Stanford Feeding Questionnaire Parental Feeding Problems scales (SFQ-PFP),³⁵ and Parents versus ARFID scale (PvARFID).³⁶
- Patients will complete: Child and Adolescent Mindfulness Measure (CAMM),^{37, 47} Body Awareness Questionnaire (BAQ),^{39, 43} Dietary Screener Questionnaire (DSQ),^{43, 48} Therapy Suitability and Acceptability Scale,¹⁷ and Assessment Acceptability Scale.

- Final Assessment 3-months post intervention

This assessment includes surveys only and will take approximately 20 minute to complete.

REDCap Surveys:

The online surveys for this assessment will be emailed to the participant and parent to be completed over the course of 1 week.



- Parents will complete: Stanford Feeding Questionnaire ARFID (SFQ-ARFID),³⁵ Stanford Feeding Questionnaire Parental Feeding Problems scales (SFQ-PFP),³⁵ and Parents versus ARFID scale (PvARFID).³⁶
- Patients will complete: Child and Adolescent Mindfulness Measure (CAMM),^{37, 47} Body Awareness Questionnaire (BAQ),^{39, 43} Dietary Screener Questionnaire (DSQ),^{43, 48} and Assessment Acceptability Scale.

6.2.5 Completion/Final Evaluation

The final assessment occurs 3-months post-intervention and is described in section 6.2.4

6.2.6 Compensation:

Compensation will be provided in the form of a check for completion of all assessment visits (baseline and follow-up visits occurring at treatment sessions 5, 10, 15, and 20 and a final assessment), for a total of \$150 to the patient and \$50 to the parent for all study visits. Participants and parents who do not complete all assessments will receive compensation for the assessments completed. Parents may choose to have their compensation check written to their child, if preferred

- Baseline: patient - \$30; parent - \$10
- Session 5: patient - \$15; parent - \$5
- Session 10: patient - \$30; parent - \$10
- Session 15: patient - \$15; parent - \$5
- Session 20: patient - \$30; parent - \$10
- Final Assessment: patient - \$30; parent - \$10

6.2.7 End-of-Study Definition

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or has dropped from the study.

7. SAFETY ASSESSMENTS

7.1 Specification of Safety Parameters

Screening procedures will include using the C-SSRS to assess for suicidality and an interview to assess psychiatric diagnoses. Study clinicians will assess self-harm, suicidal and homicidal ideation (“Have you experienced any thoughts about self-harm or suicide since we met last? Have you thought about hurting anyone else?”) with participants in each session. Any change in risk will be reported to Dr. Sysko and Dr. Freidl to review plans for additional monitoring. Dr. Sysko will monitor the ongoing progress of participants with contingencies for suicidality and worsening of symptom. Participants in the study will be withdrawn and referred for higher levels of care (e.g., outpatient or day treatment or hospitalization) as required by the psychiatric condition



or in instances of emergent psychiatric situations. Dr. Sysko will also be notified of any attrition (missed visits or study withdrawals) on a weekly basis by the study research assistant and/or post-doctoral fellow. If a safety issue is present, Dr. Sysko (the PI) will immediately notify the IRB according to the reporting. All adverse events will be reported in annual progress reports.

7.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

The CSSRS will be administered at screening and adverse events will be assessed at all study visits.

7.3 Adverse Events and Serious Adverse Events

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related.

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

The CSSRS will be administered at screening and adverse events will be assessed at all study visits. Documentation will be provided in the tracking for the respective participant.

Severity:

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".



Relation

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as “possibly related” soon after discovery, it can be flagged as requiring more information and later be upgraded to “probably related” or “definitely related”, as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

Expectedness



The expected/anticipated AEs are those described in the study documents including this protocol and the consent form. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

7.4 Reporting Procedures

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. This will be documented in an AE CRF and entered in REDCap. Baseline values used for comparison are located in the REDCap tracking database.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

Research staff will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

SAE Reporting:

Serious Adverse Events will be brought to the attention of the PI within 24 hours of the study team becoming aware. The IRB will be notified of SAEs within 5 business days. All serious adverse events (SAEs) will be followed until satisfactory resolution or until the PI deems the event to be chronic or the participant is stable.

7.5 Followup for Adverse Events

All adverse events will be followed until satisfactory resolution or until the PI deems the event to be chronic or the participant is stable. Specifically, the outcome of AEs and SAEs will be recorded at 7 and 30 days post-awareness of the events.

7.6 Safety Monitoring

Data and Safety Monitoring Plan



As this project is not a multi-site clinical trial involving an intervention that entail potential risk to the participants, we have not established a data safety monitoring board; however, the Data and Safety Monitoring Plan is described below:

The Icahn School of Medicine at Mount Sinai Institute Institutional Review Board (IRB) will assume the primary role in advising and monitoring the design and implementation of all safety monitoring and risk management procedure. More specifically, the IRB will monitor the safety of human subjects in the proposed project by reviewing: implementation of consent procedures, application of study inclusion/exclusion criteria, compliance with required clinical and administrative documentation, adverse events reporting, and adherence to specified monitoring procedures.

Active screening will be conducted for targeted conditions of interest (e.g., hospitalization, suicidal ideation) to detect changes in safety data. Clinical assessment of symptoms that could lead to or constitute adverse events (e.g., food refusal, suicidal ideation, intent, or plan) will occur during treatment. Specifically, for individuals who are not on their typical growth trajectory and need to gain weight, body weight is measured at each visit, and of acute changes in psychiatric status (i.e., suicidal and homicidal ideation) by the treating clinician in every treatment session. Elevated risk will be managed immediately upon detection, and a plan created with patient and parent(s).

Any serious or non-serious adverse event will be recorded in the participant's study folder and adverse event log and reviewed by the Mount Sinai Principal Investigator (PI; Dr. Sysko). Dr. Sysko will immediately notify the IRB regarding serious adverse events that occur within 5 business days of becoming aware of the event. The NCCIH Project Officer will be notified of SAEs within 24 hours of the IRB response. As below, all adverse events will be completely described in annual progress reports to the National Institute of Health and continuing submissions to the IRB.

As required for data and safety monitoring for NCCIH, an Independent Monitoring Committee (IMC) will remotely monitor participant safety by reviewing interim and final data and recommending whether any adaptations to the study procedures are recommended to prevent adverse occurrences with future participants. The IMC will meet twice per year, and will not be appointed until the completion of peer review as per NCCIH guidance to avoid potential conflicts of interest.

See section 7.3 for definitions of AE classification and relation.
Criteria for Stopping or Modifying Treatment or Early Termination of the Study in Relation to the AE Grading Scale: If any deviation occurs during the study that is unexpected and falls outside the normal range or in which the physician judges to be serious, the study will be terminated and emergency procedures will be initiated. An adverse event will be reported as required by the institutional IRB policy.

Study Stopping Rule



Hospitalizations due to AEs: Based on our previous research studies, we anticipate that 5-11% of the participants may need to be hospitalized due to study participation/intervention-related adverse events throughout the study. We will continuously monitor the hospitalization rate and accrual will be halted if there is sufficient evidence that hospitalization exceeds the unacceptable rate of 16%. If the cumulative number of patients hospitalized is greater than the associated boundary value b_k listed in the table below, among the k patients enrolled in the trial, then accrual will be halted for safety considerations.

Study Stopping Rule with Boundaries

| # of accrued subjects, k | 0-16 | 17-28 | 29-40 |
|----------------------------|------|-------|-------|
| Boundary, b_k | 2 | 3 | 4 |

Specifically, if **more** than 2 of the first 16 patients or more than 3 of the first 28 is hospitalized, the trial will be halted for safety considerations.

The operating characteristics of study stopping rule are as follows:

| | True Hospitalization Rate | | | |
|-------------------------------|---------------------------|------|------|------|
| | 4% | 8% | 10% | 16% |
| Probability of Early Stopping | 0.06 | 0.38 | 0.58 | 0.93 |

Using these boundaries, if the true hospitalization rate is 4%, 8%, 10%, or 16%, the probability of stopping the trial early for safety concerns is 0.06, 0.38, 0.58, and 0.93, respectively.

Protection Against Study Risks

Dr. Sysko will monitor participants with contingencies for suicidality, undisclosed psychiatric conditions, and worsening of symptoms during participation. Participants in the study will be withdrawn and referred for higher levels of care (e.g., outpatient or day treatment or hospitalization) as required by the psychiatric condition or in instances of emergent psychiatric situations. A pre-existing safety plan developed by the study MD, Dr. Freidl, a board certified child psychiatrist, will be followed in the case of an adverse or serious adverse event. Study clinicians are credentialed within the Mount Sinai Health System and have admitting privileges. If possible, Dr. Freidl will provide a warm hand-off to clinical services at our institution or the next level of care. When patients are transported by ambulance from our program (e.g., patient determined to be a safety risk to self or others), paramedics determine the location of transport and it may not be possible to contact staff at another local hospital prior to the patient arriving in those cases. When patients require a higher level of care per our safety plan, non-study related clinicians can make an independent evaluation and treatment plan for each adolescent, rather than the study team doing so in a research context, in order to avoid therapeutic misconception.



Adverse events will be handled by immediately stopping any testing and monitoring the subject (including signs, symptoms, and blood pressure) as necessary, with immediate medical assistance available through hospital resources (i.e. transporting patient to the ER) if necessary. The PI (Dr. Sysko) will also review and monitor the safety data in weekly meeting with the study team, in the aggregate on a yearly basis, and consult with the Independent Monitoring Committee (Dr. Deborah Glasofer, Associate Professor of Clinical Medical Psychology at the Columbia Center for Eating Disorders of the New York State Psychiatric Institute/Columbia University Vagelos College of Physicians and Surgeon; Dr. Robert Jaffe, Attending Psychiatrist and Assistant Professor in Psychiatry and Pediatrics at the Icahn School of Medicine at Mount Sinai; and Dr. Kristin Javaras, an Assistant Psychologist at McLean Hospital and an Assistant Professor at Harvard Medical School.

Informed Consent Process

Research study staff will obtain volunteer consent in accordance with guidelines established by the Mount Sinai IRB during the first study visit. Subjects can be sent the consent form in advance to increase the time to read through the procedures and ask questions. Volunteers are encouraged to ask questions and are reminded that participation is strictly voluntary and will not affect their current or future care in the Mount Sinai Health System.

Frequency of Data and Safety Monitoring

The PI will be responsible for monitoring the completeness of all data and source documents and ensuring that the informed consent procedures in accordance with the approved IRB procedures. The subject's data/protocol adherence will be monitored by the study team with reports provided to the PI at each step in the study. Checklists and note pages are used to note any deviations or omissions from the protocols. Dr. Sysko will also be notified of any attrition (missed visits or study withdrawals) on a weekly basis by the study project manager and/or post-doctoral fellow. The study staff has made every effort to recognize risks and ensure the safety of program participants.

Privacy and Confidentiality

Maintaining participants' privacy and keeping personal identifiers confidential is important to the study staff. All research activity, including screening and data collection, will be performed at the Eating and Weight Disorders Program at Mount Sinai. Subject names, contact information, health history, and other information that can be traced back to the subject will be kept separately from data collected for the study. Personal information will be kept in a locked office and away from data. Collected data will have the subject's identification code and some computer software used to collect data will have the date and time marked on the file. Protocol sheets used during data collection will only have the subject's ID. Data shared with the National Data Archive will only include de-identified data. Key personnel have completed education on the use of human subjects in compliance with NIH regulations.



8. INTERVENTION DISCONTINUATION

Intervention Discontinuation:

Discontinuation from MBIE sessions does not mean discontinuation from the follow-up assessments, which will still be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE). The reason for discontinuation will be collected at the time of study intervention discontinuation.

Participant Discontinuation:

Participants are free to withdraw from participation in the study at any time upon request. This will not affect their ability to receive medical care at any of the Mount Sinai Health System hospitals or receive any benefits to which they are otherwise entitled. If a subject decides to stop being in the research study, they must contact the Principal Investigator or the research staff and provide written documentation of their intent to end their participation. Even if a subject withdraws permission, the Principal Investigator for the research study may still use the information that was already collected if that information is necessary to complete the research study. Any health information may still be used or shared after a subject withdraws authorization if he/she has an adverse event from participating in the research study.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy (self-reported)
- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Worsening of psychiatric conditions such that participant would be clinically better served by referral for other treatment

The reason for participant discontinuation or withdrawal from the study will be recorded. If a participant is removed or withdraws from the intervention, and it is appropriate/feasible to continue with the follow-ups, they will be invited to continue



completing follow-up appointments. Subjects who sign the informed consent form and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

Lost to Follow-up:

Participants will be considered lost to follow-up if they withdraw from the study directly by contacting the research team or if they don't complete the entirety of their visits. Participants will be contacted via phone and email throughout the study timeline to maintain the assigned visit schedule and complete procedures. If no contact is made during the window, they will be deemed lost to follow-up.

9. STATISTICAL CONSIDERATIONS

9.1 General Design

Aim 1: Feasibility of Trial Enrollment, Treatment Tolerability, Drop Out, and Adverse Events

No formal hypothesis testing. Results are descriptive for trial development and planning. We will use go/no-go response based on 95% CI excluding 5 on VAS scales of treatment tolerability and acceptability to determine motivation for treatment refinement or motivating larger trial.

Aim 2: Feasibility of Treatment Fidelity Assessment

No formal hypothesis testing of treatment acceptability. Results are descriptive for evaluation treatment feasibility. We will test the relationship between acceptability and change in our primary symptom measures.

We hypothesize that acceptability will correlate with change in:

- a. $\beta \neq 0$ ARFID symptom score
- b. $\beta \neq 0$ Disgust bias
- c. $\beta \neq 0$ Food Disgust extinction
- d. $\beta \neq 0$ Childhood Mindfulness
- e. $\beta \neq 0$ Nonjudgement body awareness
- f. $\beta \neq 0$ Food Frequency (autonomous eating)
- g. $\beta \neq 0$ Stanford Feeding Questionnaire
- h. $\beta \neq 0$ Parental self-efficacy (Parent's vs ARFID).

Aim 3: Dose response of MBIE and Exposure on functional food avoidance.

We hypothesize that:

- a. The relationship between # sessions (dose) and function food avoidance will be significantly different than 0 (b parameter).



- a. The relationship between exposure level on food hierarchy (1-10) will be significantly different than 0 (b parameter).

We hypothesize that 20 sessions of MBIE will yield reliable change in primary and mechanistic targets.

Reliable change in:

- a. ARFID symptoms (SFQ)
- b. Disgust Bias (go/no go)
- c. Food Disgust Extinction Learning
- d. Child and Adolescent Mindfulness Measure
- e. Nonjudgmental Body Awareness
- f. Dietary Screener Questionnaire (Avoidance)
- g. Functional Food Hierarchy
- h. Functional Food Avoidance
- i. Stanford Feeding Questionnaire
- j. Parental Efficacy (Parents vs ARFID scale)

In this single-site trial, we will use a phase I, non-randomizing, dose-optimizing (20 sessions) clinical trial design to examine feasibility and appropriate duration of treatment for a cohort of N=57 enrolled (N=40 completers) youth ages 12-18 with ARFID. Interview, self-report, anthropometrics, laboratory feeding, and behavioral task data will be used to characterize the sample to their response to treatment over time. Follow-up assessments will be completed at session 5, 10, 15, and 20. Total participant will last 6 months.

9.2 Sample Size and Randomization

Statistical power was not formally calculated for this feasibility design. For within-subject effects (Aim 3), we note that when the sample size is 11, the multiple linear regression test of $\rho^2 = 0$ ($\alpha = 0.05$) for 2 normally distributed covariates (baseline, age) will have 80% power to detect a ρ^2 of 0.6. With the planned sample of N = 40, we will be 80% powered to detect a ρ^2 of 0.2. Thus, the sample size of N = 40 will allow us to reasonably estimate feasibility requirements for Aim I (recruitment rate, dropout rate, safety/AEs), but also generate a reasonable estimate of within subject changes in our symptom measures (Aim 3). Power calculations for primary and secondary outcomes were estimated using nQuery software (2022).⁴⁹ We will also calculate within-subject effect sizes as a measure of clinical change using the reliable change index (RCI),⁵⁰ calculate variance, point estimates (mean/median), and distribution for slopes (change/time) to inform power and design of future clinical trials and identify mechanistic targets (mechanisms that demonstrate reliable change). For our dose-response aims (Aim 3), we anticipate a 4-parameter logistic model will be the most appropriate for the data. We estimated power using sigma ranging from 0.15 to 0.3 and with sample size of N=40, we are 0.8 powered to detect dose-response effects with maximum treatment effect of 0.2, which is well within the target effect



size of $d = 0.55$ for our primary outcome (reduction in functional food avoidance of $M = 25$, $SD = 35$, $\text{corr} = 0.2$) on the 0-100 scale of functional food avoidance. Consequently, we are well powered to detect a significant dose response relationship with $N = 40$, $\alpha = 0.05$, and dose ranges from 0-20, and expected reduction in functional food avoidance of 25 points on 0-100 scale with $SD = 35$; however, this is a very conservative estimate, as our clinical experience with this population indicates a much larger reduction in functional food avoidance than 25 points. The same formula and power estimate applies for the secondary dose response model where dose will be the 10 levels of the Functional Food Hierarchy.

9.3 Definition of Populations

Based on the specifications of this RFA, the study is not focused on efficacy (treatment vs. control), but within subject change relative to the amount of treatment (i.e. dose). We will analyze an intent-to-treat sample and calculate standardized mean differences (SMDs) for within-subject change for all of our feasibility and clinical outcomes, but the expected effect size for within-subject change is moderate, equating to a 50% reduction in functional food avoidance (i.e., $d = 0.5$). We will examine this weekly outcome relative to other mechanistic and global symptom measures to ensure the treatment has additional effects on affect and functioning. Variability estimates in these within-subject SMDs will provide critical information for the planning of any future research (e.g., efficacy trial and/or mechanistic trials) for the target population.

9.4 Interim Analyses and Stopping Rules

If the benefit-risk analysis of this study changes based on the number of SAEs related to study procedures, we will consult with the IRB and determine how to proceed (e.g., changes to the inclusion criteria, additional criteria for discontinuation of research participation, ending the trial prematurely).

9.5 Outcomes

For Aims I & II, we will use descriptive statistics to characterize:

Volume:

(Screened/Enrollment)/time, and characterize the relationship between recruitment strategies and enrollment. These data will be used to generate point estimates and confidence intervals for projected recruitment rates in larger trials.

Tolerability/Acceptability:

Unintended negative effects of the treatment will be calculated from the Therapy Suitability and Expectancy Scale which yields scores from 0-10 (derived from average of VAS scaled items). Means (SD) and 95% CI for point estimates will be estimated from the sample at each planned assessment point (BL, 5-week, 10-Week, 15-week, 20-week). A session-response curve will be estimated for the 4 intervals assessed. With an anticipated $SD = 2$, and within-subject correlations of 0.5 (suggesting a high degree of reliability in tolerability and acceptability, our go-no go



criteria for the intervention will be 95%CI interval that does not include a score of 5 on the given TSES scale. Failure of the treatment to achieve tolerability and acceptability above 5 will lead to treatment model refinement before pursuing mechanistic or efficacy studies.

Drop out:

We will estimate count of drop out/completion with 95% CI for population estimates of expected dropout with > 30% dropout leading to further treatment and enrollment refinement before additional study.

Adverse Events:

We will calculate the frequency of each individual adverse event characterized and total adverse events over the course of treatment. Study stopping rules are detailed in the data safety monitoring plan and will be estimated by severity and type, with boundaries crossing leading to consultation with safety monitor to determine whether to stop or alter study or procedures.

Treatment Fidelity:

We will use a time series Bayesian Belief Network (BBN)¹¹⁴ characterizing individually coded therapy sessions using our developed fidelity measures for MBIE.⁹⁷ This model will generate 20 families x 10 sessions = 200 (low dose fidelity) and 20 families x 20 sessions = 400 (high dose fidelity) measures. Each assessment yields 3 domain scores (adherence, competency, and divergence). In the time series extension of a BBN, these three ratings are dependent upon prior level (lag 1) and the autoregressive effect can be conceptualized as stability of the estimates. The model building and estimation will be done using bnlearn⁵¹ and estimated with the with Markov blanket using 10-fold cross validation with Min-Max Hill-Climbing algorithm. 80% fidelity criteria under investigation will be established by calculating individual fidelity scores from the network model and scaling 0-1. We will then establish a point-estimate of fidelity for each individual/sessions.

For Aim III, we are using 4 parameter logistic model and will use the following form:

$$Y = d + \frac{a - d}{1 + \left(\frac{x}{c}\right)^b}$$

Where

x = dose (# sessions or exposure level on functional hierarchy, and Y = function food avoidance (0100).

a = minimum value of Y at dose 0

b = Hill's slope of the curve or steepness of the curve at point c.

c = inflection point (halfway point between a – d)

d = maximum value of Y at dose infinity

The estimates of these parameters we will use the hierarchical model derived from medrc package⁵² which utilizes a maximum likelihood estimate of random effects (slope and intercept) using the Lindstrom-Bates algorithm. We will use traditional models of fit (AIC,-2LL, BIC)⁵³ to examine whether full mixed models are necessary and determine if level 2 covariates (age, race/ethnicity, parent functioning) offer



improved fit. We will have 20 within treatment assessment points (20-repeated measures on level 1). As this is a pilot trial, it is possible that with a small sample there will be a convergence issue or difficulty detecting covariate effects; however, the study was powered for repeated measures with 40 patients, and we do not expect there to be a pattern of data with a high degree of variability (e.g., chaos) given that we are sampling from a homogeneous population.

The equation above will be modified for autonomous eating and to account for greater dispersion and nonnormal fit to these data. There are many choices ranging from lognormal and Tweedie continuous solutions to exponential family models such as negative binomial to account for skewed density of the probability mass and long tails. Given our experience and the majority of published data using our meal paradigm or similar procedures and individuals with feeding or eating disorders, we plan on using a gamma distribution, with location and scale parameters and we will incorporate time since last meal and meal type, as time varying covariates into equation (1) above.

$$Y_{ij} = \text{Gamma}(y_{ij} | \lambda_{ij}, \alpha)$$

Where

$$Y_{ij} = \text{Gamma}(y_{ij} | \lambda_{ij}, \alpha) = \frac{1}{\alpha^{\lambda_{ij}} \Gamma(\lambda_{ij})} y_{ij}^{\lambda_{ij}-1} \exp\left(-\frac{y_{ij}}{\alpha}\right)$$

For the extinction learning model, we will use an adaptation of the model above, where we integrate ordinal outcomes of extinction (behavioral choice to Yucky, Neutral, Yummy [-1, 0, 1]) on the ordinal scale. The function link for ordinal regression uses:

$$\text{logit}(P(Y \leq j))$$

to link Y_{ij} to equations 1-3 above. The d-prime measure of disgust bias will be estimated using the continuous GLM noted above.

Validation of the laboratory feeding model will be carried out by automated emotional scoring of laboratory meal using FaceReader software.⁵⁴⁻⁵⁶ We will model the dynamic relationship between disgust (as scored by FaceReader AI) and sips of the meal replacement shake. To control for possible negative affect bias, we will average other negative affect (sad, angry, scared) and positive affect (happy, joy) signals. This yields a model with 3 continuous time variables (negative affect, disgust, positive affect) and one event related variable (sip of shake). The laboratory meal test of autonomous eating lasts 15 min and the video recording collects data at 17 frames per second. Consequently, there are $17 * 60 * 15$ observations 15,300 observations per individual, per timepoint. To estimate this computational model, we will use multilevel formulation of the dynamic structural equation model (DSEM).⁵⁴ To build the model, we will follow recent recommendations to evaluation simple N-1 models



for each individual with static, lagged, cross-lagged, models estimated in succession. We will then progress to two-level random effects models, where we will formally test our hypothesized relationship between disgust and feeding behavior. Using a DSEM for FaceReader with an $n=1$ model and a time-series with 17 frames per second, and prior experience analyzing this type of data (e.g., Boyar, A., Martin, E. Schulz, K., & Hildebrandt, T. (2023, June). Computational Analysis of Emotional Response to Food-Cue Reversal Learning. Poster presented at the International Conference on Eating Disorders, Washington, DC.), we expect there will be sufficient data to measure this effect. These models are estimated with Bayesian estimation and flat priors on the random effects.⁵⁷ The random intercept at the between level can be thought of as the trait level of measure as it captures the stability of the autoregressive effect per individual. The within subject lag is also estimated as a random effect at the between level and provides an estimate of lagged effects of emotion on sip and sim on emotion. This $\beta_{\text{lagDisgust}}$ parameter will be used as our validator. A significant effect at baseline will be used as evidence that (a) post-sip disgust affects likelihood of taking another sip.

In addition, we will calculate diet variety scale scores based on multi-item meals choices weighted for distress of items found on the functional food hierarchy. A simple subjective units of distress scale rating/100 weight factor will be added to each item and this weight score imported to sum foods chosen/sum of foods available to get the weighted diet variety scale.

For all models we will examine covariate effects of % Expected Body Weight, Age, Sex, and Parental Feeding to identify source variability in treatment response.

9.6 Data Analyses

General Modeling Approach. A sensitivity analysis will be performed and tests for missingness (e.g., MCAR, NMAR, and imputation) will be performed. Our MLE will use all available data. For our feasibility aims, we will generate point estimates of central tendency, variance, and measure distribution (e.g., Poisson, Gaussian, etc.) and generate estimates for the relationship between acceptability and symptoms domains using general linear model. To characterize clinical effects of MBIE, mixed effects models will examine evidence for random intercept and slope models, which will allow the identification of variance-covariance structures for planning future studies. Dose-response analyses will utilize a simple 4-parameter mixed effects (random slope/intercept) logistic model for Gaussian outcomes and we will estimate the overall fit using traditional Akaike information criterion, Bayesian information criterion, and likelihood ratio tests to compare different model parameterizations. The slope parameter will characterize relationship between session number (or hierarchy level) and response, ED50 the dose necessary for 50% response, and the remaining two parameters provide upper and lower bounds of the sigmoid curve.



Fidelity Measure. To measure fidelity, we will attempt to replicate our pilot data and estimate dynamic Bayesian belief networks⁵⁸, which includes 4 directed paths between the parent (MBIE competency) child (MBIE adherence), Competency-Differentiation, and Differentiation-Adherence. We will use the Hill Climbing 10-fold cross-validation algorithm to evaluate the model by estimating first structure, followed by parameter learning. We expect that model will generate a reasonable fit to the data, but will also calculate individual metrics of network performance (cohesion, robustness, fragility, etc.).⁵⁹ For aim 2, we will test separate models examining the predictive value of the network on Patient Suitability and Tolerability scale scores.

Laboratory Feeding. We will derive simple measures of Kcal and rate of eating from the laboratory measure, and analyze videos with FaceReader, an artificial intelligence coding of emotions. The algorithm generates a probability score (0-1) based on 18 facial vertices derived from their custom algorithm. Scores are calculated for each emotion (Sad, Scared, Angry, Disgust, Neutral, Surprise, Happy, and Joy). To validate the theoretical model, we will model relationships between food consumption and emotional expressions (and vice versa), using dynamic structural equation modeling, with random (between subject) effects for the lagged effects between feeding and disgust. Because we will also estimate random autoregressive effects, we will be controlling for trait level emotion, allowing stronger inferences that the lagged effects are evidence of relationship between disgust and feeding and feeding and disgust. As an exploratory analysis, we will extend this test to examine pre-post changes in these lagged effects.

Power Considerations. Consistent with the grant mechanism, the study is powered to estimate a dose-response model where parameters of interest, ED50, and slope are significantly different than zero. We utilized the medrc package in R to inform our sample size estimate. With 40 subjects, we have > 80% power to detect significant effects (slope) $\neq 0$, with alpha = 0.05, and sigma = .2. For within-subject effects in validation aims with the planned sample of N = 40, we will be 80% powered to detect a ρ^2 of 0.2. Thus, the sample size of N = 40 will allow a reasonable estimate of feasibility requirements for Aim I (recruitment rate, dropout rate, safety/AEs), but also generate an appropriate estimate of within subject changes in our symptom measures, and dose-response tests planned for (Aim 3). The main threat to power includes alternative dose-response models with unusual forms resulting in misspecification. We will plot individual curves and interpret random intercepts and slopes accordingly to determine if variance between individuals is too large for accurate estimates and turn to covariate analyses to determine source variability to further refine our approach to mitigate this threat.

10. DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

Screening & Baseline Assessments:



1. Height/Weight
2. Demographics
3. The EDA-5²⁹ is an adaptive online semi-structured interview used in the assessment of feeding and eating disorders based on DSM-5 criteria.
4. Columbia Suicide Rating Scale (C-SSRS)³¹ has four subscales measuring severity and intensity on a 5 point scale, behavior on a nominal scale, and lethality on a 6 point scale or 3 point if lethality is zero. Higher scores indicate higher risk of suicidal thoughts and behaviors. The C-SSRS consists of 10 binary (yes/no) categories, Category 1 – Wish to be Dead, Category 2 – Non-specific Active Suicidal Thoughts, Category 3 – Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act, Category 4 – Active Suicidal Ideation with Some Intent to Act, without Specific Plan, Category 5 –Active Suicidal Ideation with Specific Plan and Intent, Category 6 – Preparatory Acts or Behavior, Category 7 – Aborted Attempt, Category 8 – Interrupted Attempt, Category 9 – Actual Attempt (non-fatal), Category 10 – Completed Suicide. Composite endpoints are suicidal ideation, suicidal behavior, suicidal ideation or behavior. Suicidal ideation is determined by a “yes” answer in Categories 1-5, suicidal behavior is determined by a “yes” answer in Categories 6-10, and suicidal ideation or behavior is determined by a “yes” in Categories 1-10
5. Single Item Test-Meal^{60, 61} is a laboratory test to assess avoidance of food using a standardized test meal of a yogurt shake. The shake will be weighed before and after the test meal to measure consumption of the shake. Measurements will include kcal consumed, rate of eating, and emotions expressed during meal.
6. Extinction learning (food-disgust cues) is a laboratory task consisting of separate 6 minute and 40 second acquisition and extinction blocks with 20-second fixation periods included at the beginning and end of the block. Conditioned and unconditioned stimuli will be used in pairing with pictures of palatable or rotten food.
7. Go/No-Go Task⁴² is a 20-minute task that requires an individual to respond to an instructed go signal (i.e., happy faces) of faces portraying different types of emotion (happy, neutral, disgust) flashing on the screen. After each trial, participants will be re-instructed to respond to a different (or the same) go signal (i.e., happy faces). The primary measure is % correct on no-go signal tests which taps neurocircuits involved in emotion regulation.
8. Child and Adolescent Mindfulness Measure (CAMM)⁴⁷ is a 10-item measure of mindfulness skills validated in school-aged children and adolescents. Scores indicate observation of internal experiences their acceptance without judgement.³⁹
9. Body Awareness Questionnaire (BAQ)⁴³ is a self-report measure assessing awareness of body sensitivity and changes using 18 items on a score range of 18-126. Higher scores indicate more awareness of body regulation.
10. Dietary Screener Questionnaire (DSQ)⁴⁸ is a 26-item self-report measure of food consumption frequency within the past month.
11. Stanford Feeding Questionnaire-ARFID Scale (SFQ-ARFID)³⁵ is a parent questionnaire with 12 items that assess ARFID symptoms.



12. The SFQ-Parental Feeding Problems Scale (SFQ-PFP)³⁵ comprises 15 items from the Stanford Feeding Questionnaire, which evaluate parental feeding problems.
13. Parent versus Avoidant/Restrictive Food Intake Disorder (PvARFID) is modified from the Parents versus Anorexia Nervosa Scale³⁶ to measure parental self-efficacy at changing eating behaviors for ARFID.
14. Assessment Acceptability Scale: an investigator-derived measure to assess the tolerability and ease of assessment procedures administered at baseline (8 items).

Intervention Assessments:

1. Height/Weight
2. The Functional Food Avoidance Scale is made of visual analog scales from relevant domains (limited intake, limited variety, fear of aversive consequences) used to better characterize participant subtypes. Parents will also provide a rating of weekly progress with food avoidance in each of the 20 MBIE sessions to determine how many sessions are needed to reach a clinically-meaningful outcome (i.e., tolerate consuming a food rated as $\geq 70/100$ subjective units of distress in natural environment). The scale will range from 0-100, with higher scores reflecting lower avoidance/increased consumption for analyses to determine the relationship between session number (dose) and foods consumed (response).
3. Functional Food Hierarchy will be a measure created by therapists during MBIE to direct interoceptive exposure exercises. The 10 levels of the hierarchy are based on functional distress, with foods/contexts listed under each level from 10-100 on functional distress scale. This exercise, with session-by-session updates by the therapist, will also permit us to validate a score of diet variety based on the number of foods consumed during treatment adjusted by difficulty (subjective distress) and function in daily living.
4. Therapy Integrity Scales: This is an investigator-derived, adapted from forms and procedures from previous studies, which will be used to measure elements of MBIE (process, common factors that occur every session, interventions specific to each session), therapist competence, therapist differentiation (i.e., inclusion of non-treatment elements), and adherence. Each item is rated on a Likert scale on extent of use of the treatment element, and a scale on the quality of delivery of the intervention.
5. Therapy Suitability and Acceptability Scale: An MBIE-adapted Therapy Suitability and Acceptability Scale¹⁷ will average specific items from patient's view on match of therapy to the problem, responsiveness of intervention to different treatment challenges, degree of unexpected discomfort related to treatment, interest in using therapy experiences beyond the therapy session using visual analog scales (VASs; 0-10).
6. Assessment Acceptability Scale: an investigator-derived measure to assess the tolerability and ease of assessment procedures administered at session 5 (2 items), 10 (4 items), and 20 (4 items).

Follow-up Assessments:



| Measures | Baseline / Screening | Session 5 | Session 10 | Session 15 | Session 20 | Final |
|---|----------------------|-----------|------------|------------|------------|-------|
| EDA-5 | X | | | | | |
| C-SSRS | X | | | | | |
| Therapy Suitability/Acceptability, Assessment Acceptability | X | X | X | X | X | X |
| Height/Weight | X | X | X | X | X | |
| SFQ-ARFID Scale | X | X | X | X | X | X |
| SFQ-PHP Scale | X | X | X | X | X | X |
| PvARFID | X | X | X | X | X | X |
| CAMM | X | X | X | | X | X |
| BAQ | X | X | X | | X | X |
| DSQ | X | X | X | | X | X |
| Extinction Learning | X | | | | | |
| Disgust Bias (Go/No-go) | X | | | | | |
| Single Item Meal | X | | X | | X | |

Documentation methods:

The following will be documented on CRF forms by research staff and then entered into the REDCap tracking database:

- EDA-5 outcome
- C-SSRS
- Height/Weight
- Inc/Exclusionary data
- SIM data

The following will be documented stored in the program used to run the assessment:

- Extinction Learning
- Disgust Bias (Go/No-go)

The following will be entered into REDCap directly by the participant/parent:

- SFQ-ARFID Scale
- SFQ-PHP Scale
- PvARFID
- CAMM
- BAQ
- DSQ
- Extinction Learning



- Disgust Bias (Go/No-go)
- Single Item Meal
- Functional Food Avoidance Scale
- Functional Food Hierarchy
- Therapy Integrity Scales
- Therapy Suitability and Acceptability Scale

10.2 Data Management

Data collection forms include CRF's and REDCap surveys. The PI and project manager will review consent forms and regulatory binders on a quarterly basis.

The research delegate and project manager will review all consent forms after signing to ensure that they were properly signed and completed.

The data will be stored for 7 years following data analysis/publication, as per Mount Sinai policy.

10.3 Quality Assurance

10.3.1 Training

All research staff will be trained on study procedures prior to study initiation.

10.3.2 Quality Control Committee

Dr. Robyn Sysko will conduct all data safety monitoring monthly with the research team. We will conduct monthly data audits to evaluate the quality of the data entered and to ensure missing data or data entry errors are avoided. The process involves reviewing individual case data, interview data, psychometric data, and biometric data.

- Informed Consents: Study staff will review both the documentation of the consenting process as well as a percentage of the completed consent documents. This review will evaluate compliance with GCP, accuracy, and completeness. Feedback will be provided to the study team to ensure proper consenting procedures are followed.
- Protocol Deviations: The study team will review protocol deviations on an ongoing basis and will implement corrective actions when the quantity or nature of deviations are deemed to be at a level of concern.
- Source Documents and Electronic Data: Any data that is initially captured on source documents and is ultimately entered into the study database will be compared by using a representative sample targeting key data points in the review.

Should independent monitoring become necessary, the PI will provide direct access to all trial related sites, source data/documents, and reports for the purposed of



monitoring and auditing by the sponsor/funding agency, and inspection by local regulatory authorities.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 7 working days of identification of the protocol deviation, or within 7 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents. Protocol deviations will be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

11. PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

This protocol, informed consent document, modifications, and participant-facing forms will be reviewed and approved by the IRB or ethics committee responsible for oversight of the study.

11.2 Informed Consent Forms

The procedures for obtaining and documenting informed consent of study participants and vulnerable populations is mentioned in section 6.2.1

11.3 Participant Confidentiality

To protect confidentiality, the following precautions will be taken:

- All research activities will be conducted in as private a setting as possible.
- All questionnaire and interview data will use study identification numbers
- Electronically stored data will be coded and password protected in a secure database behind the Mount Sinai Firewall
- All identifying paper information will be stored in a locked file cabinet and will be available only to research staff

11.4 Study Discontinuation

The study may be discontinued at any time by the IRB, the NCCIH, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research participants are protected.

12. COMMITTEES

N/A

13. PUBLICATION OF RESEARCH FINDINGS

This study will be conducted in accordance with the following publication and data



sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers x years after the completion of the primary endpoint by contacting <specify person or awardee institution, or name of data repository>.

In addition, this study will comply with the NIH Genomic Data Sharing Policy, which applies to all NIH-funded research that generates large-scale human or non-human genomic data, as well as the use of these data for subsequent research. Large-scale data include genome-wide association studies (GWAS), single nucleotide polymorphisms (SNP) arrays, and genome sequence, transcriptomic, epigenomic, and gene expression data.

15. SUPPLEMENTS/APPENDICES

Future Use of Stored Specimens and Data

The proposed study data is for research purposes only. Only trained and qualified research team members will have access to study data. To further reduce possible risk to participants, all paper data will be stored in locked file cabinets and electronic data on password-protected systems. Participants will be assigned a study code, which is the only identifier used when labelling study data.

The data will be stored for seven years following data analysis/publication, as per Mount Sinai policy.

Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the Icahn School of Medicine has established policies and procedures for all study group members to disclose all conflicts of interest and



will establish a mechanism for the management of all reported dualities of interest.

14. REFERENCES

1. Hofmann SG, Asmundson GJG. Acceptance and mindfulness-based therapy: new wave or old hat? *Clin Psychol Rev*. Jan 2008;28(1):1-16. doi:10.1016/j.cpr.2007.09.003
2. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders (5th ed.)*. 2013
3. Bryant-Waugh R. Avoidant/Restrictive Food Intake Disorder. *Child Adolesc Psychiatr Clin N Am*. Oct 2019;28(4):557-565. doi:10.1016/j.chc.2019.05.004
4. Kurz S, van Dyck Z, Dremmel D, Munsch S, Hilbert A. Early-onset restrictive eating disturbances in primary school boys and girls. *Eur Child Adolesc Psychiatry*. Jul 2015;24(7):779-85. doi:10.1007/s00787-014-0622-z
5. Fisher MM, Rosen DS, Ornstein RM, et al. Characteristics of avoidant/restrictive food intake disorder in children and adolescents: a "new disorder" in DSM-5. *J Adolesc Health*. Jul 2014;55(1):49-52. doi:10.1016/j.jadohealth.2013.11.013
6. Eddy KT, Thomas JJ, Hastings E, et al. Prevalence of DSM-5 avoidant/restrictive food intake disorder in a pediatric gastroenterology healthcare network. *Int J Eat Disord*. Jul 2015;48(5):464-70. doi:10.1002/eat.22350
7. Nicely TA, Lane-Loney S, Masciulli E, Hollenbeak CS, Ornstein RM. Prevalence and characteristics of avoidant/restrictive food intake disorder in a cohort of young patients in day treatment for eating disorders. *J Eat Disord*. 2014;2(1):21. doi:10.1186/s40337-014-0021-3
8. Ornstein RM, Rosen DS, Mammel KA, et al. Distribution of eating disorders in children and adolescents using the proposed DSM-5 criteria for feeding and eating disorders. *J Adolesc Health*. Aug 2013;53(2):303-5. doi:10.1016/j.jadohealth.2013.03.025
9. Chandran JJ, Anderson G, Kennedy A, Kohn M, Clarke S. Subacute combined degeneration of the spinal cord in an adolescent male with avoidant/restrictive food intake disorder: A clinical case report. *Int J Eat Disord*. Dec 2015;48(8):1176-9. doi:10.1002/eat.22450
10. Tsai K, Singh D, Pinkhasov A. Pudendal nerve entrapment leading to avoidant/restrictive food intake disorder (ARFID): A case report. *Int J Eat Disord*. Jan 2017;50(1):84-87. doi:10.1002/eat.22601
11. Nakai Y, Nin K, Noma S, et al. Clinical presentation and outcome of avoidant/restrictive food intake disorder in a Japanese sample. *Eat Behav*. Jan 2017;24:49-53. doi:10.1016/j.eatbeh.2016.12.004
12. Strandjord SE, Sieke EH, Richmond M, Rome ES. Avoidant/Restrictive Food Intake Disorder: Illness and Hospital Course in Patients Hospitalized for Nutritional Insufficiency. *J Adolesc Health*. Dec 2015;57(6):673-8. doi:10.1016/j.jadohealth.2015.08.003
13. Hay P, Mitchison D, Collado AEL, Gonzalez-Chica DA, Stocks N, Touyz S. Burden and health-related quality of life of eating disorders, including Avoidant/Restrictive Food Intake Disorder (ARFID), in the Australian population. *J Eat Disord*. 2017;5:21. doi:10.1186/s40337-017-0149-z
14. Norris ML, Robinson A, Obeid N, Harrison M, Spettigue W, Henderson K. Exploring avoidant/restrictive food intake disorder in eating disordered patients: a descriptive study. *Int J Eat Disord*. Jul 2014;47(5):495-9. doi:10.1002/eat.22217
15. Thomas JJ, Lawson EA, Micali N, Misra M, Deckersbach T, Eddy KT. Avoidant/Restrictive Food Intake Disorder: a Three-Dimensional Model of Neurobiology with



- Implications for Etiology and Treatment. *Curr Psychiatry Rep.* Aug 2017;19(8):54. doi:10.1007/s11920-017-0795-5
16. Sharp WG, Volkert VM, Scahill L, McCracken CE, McElhanon B. A Systematic Review and Meta-Analysis of Intensive Multidisciplinary Intervention for Pediatric Feeding Disorders: How Standard Is the Standard of Care? *J Pediatr.* Feb 2017;181:116-124 e4. doi:10.1016/j.jpeds.2016.10.002
 17. Lock J, Sadeh-Sharvit S, L'Insalata A. Feasibility of conducting a randomized clinical trial using family-based treatment for avoidant/restrictive food intake disorder. *Int J Eat Disord.* Jun 2019;52(6):746-751. doi:10.1002/eat.23077
 18. Boettcher H, Barlow DH. The unique and conditional effects of interoceptive exposure in the treatment of anxiety: A functional analysis. *Behav Res Ther.* Jun 2019;117:65-78. doi:10.1016/j.brat.2018.12.002
 19. Barlow DH. Unraveling the mysteries of anxiety and its disorders from the perspective of emotion theory. *Am Psychol.* Nov 2000;55(11):1247-63. doi:10.1037//0003-066x.55.11.1247
 20. Craske MG, Rowe M, Lewin M, Noriega-Dimitri R. Interoceptive exposure versus breathing retraining within cognitive-behavioural therapy for panic disorder with agoraphobia. *Br J Clin Psychol.* Feb 1997;36(1):85-99. doi:10.1111/j.2044-8260.1997.tb01233.x
 21. Boettcher H, Brake CA, Barlow DH. Origins and outlook of interoceptive exposure. *J Behav Ther Exp Psychiatry.* Dec 2016;53:41-51. doi:10.1016/j.jbtep.2015.10.009
 22. Craske MG, Wolitzky-Taylor KB, Labus J, et al. A cognitive-behavioral treatment for irritable bowel syndrome using interoceptive exposure to visceral sensations. *Behav Res Ther.* Jun 2011;49(6-7):413-21. doi:10.1016/j.brat.2011.04.001
 23. Ljotsson B, Andreevitch S, Hedman E, Ruck C, Andersson G, Lindefors N. Exposure and mindfulness based therapy for irritable bowel syndrome--an open pilot study. *J Behav Ther Exp Psychiatry.* Sep 2010;41(3):185-90. doi:10.1016/j.jbtep.2010.01.001
 24. Bouton ME, Mineka S, Barlow DH. A modern learning theory perspective on the etiology of panic disorder. *Psychol Rev.* Jan 2001;108(1):4-32. doi:10.1037/0033-295x.108.1.4
 25. Eddy KT, Thomas JJ. Introduction to a special issue on child and adolescent feeding and eating disorders and avoidant/restrictive food intake disorder. *Int J Eat Disord.* Apr 2019;52(4):327-330. doi:10.1002/eat.23052
 26. Gutierrez R, Fonseca E, Simon SA. The neuroscience of sugars in taste, gut-reward, feeding circuits, and obesity. *Cell Mol Life Sci.* Sep 2020;77(18):3469-3502. doi:10.1007/s00018-020-03458-2
 27. Berridge KC. Food reward: brain substrates of wanting and liking. *Neurosci Biobehav Rev.* 1996;20(1):1-25. doi:10.1016/0149-7634(95)00033-b
 28. Brown MH, T. Parent-Facilitated Behavioral Treatment for Avoidant/Restrictive Food Intake Disorder: A Case Report. *Cognitive and Behavioral Practice.* 2019;27
 29. Sysko R, Glasofer DR, Hildebrandt T, et al. The eating disorder assessment for DSM-5 (EDA-5): Development and validation of a structured interview for feeding and eating disorders. *Int J Eat Disord.* Jul 2015;48(5):452-63. doi:10.1002/eat.22388
 30. Nazar BP, Gregor LK, Albano G, et al. Early Response to treatment in Eating Disorders: A Systematic Review and a Diagnostic Test Accuracy Meta-Analysis. *European Eating Disorders Review.* 2017;25(2):67-79. doi:<https://doi.org/10.1002/erv.2495>
 31. Posner K, Brent D, Lucas C, et al. Columbia Suicide Rating Scale (CSSRS) Children's Baseline Screening Version. 2010



32. Baer RA FS HD. Mindfulness and acceptance in the treatment of disordered eating. *Journal of Rational-Emotive & Cognitive-Behavior Therapy*. 2005;
33. Kristeller JL BR Q-WR. *Mindfulness-based approaches to eating disorders*. . In: Baer R, ed. *Mindfulness-based treatment approaches: clinician's guide to evidence base and applications*. Elsevier Academic Press; 2006.
34. Kristeller JL, Wolever RQ. Mindfulness-based eating awareness training for treating binge eating disorder: the conceptual foundation. *Eat Disord*. Jan-Feb 2011;19(1):49-61. doi:10.1080/10640266.2011.533605
35. Jacobi C, Agras WS, Bryson S, Hammer LD. Behavioral validation, precursors, and concomitants of picky eating in childhood. *J Am Acad Child Adolesc Psychiatry*. Jan 2003;42(1):76-84. doi:10.1097/00004583-200301000-00013
36. Rhodes P, Baillie, A., Brown, J., & Madden, S. . Parental efficacy in the family-based treatment of anorexia: Preliminary development of the parents versus anorexia scale (PVA). . *European Eating Disorders Review*. 2005;13(6):399–405.
37. Shafritz KM, Collins SH, Blumberg HP. The interaction of emotional and cognitive neural systems in emotionally guided response inhibition. *Neuroimage*. May 15 2006;31(1):468-75. doi:10.1016/j.neuroimage.2005.11.053
38. Hildebrandt T, Bacow T, Markella M, Loeb KL. Anxiety in anorexia nervosa and its management using family-based treatment. *Eur Eat Disord Rev*. Jan 2012;20(1):e1-16. doi:10.1002/erv.1071
39. Bender SL, Lawson T, Palacios AM. Mindfulness Measures for Children and Adolescents: a Systematic Review. *Contemporary School Psychology*. 2022/10/13 2022;doi:10.1007/s40688-022-00433-5
40. Baer RA, Smith GT, Hopkins J, Krietemeyer J, Toney L. Using self-report assessment methods to explore facets of mindfulness. *Assessment*. Mar 2006;13(1):27-45. doi:10.1177/1073191105283504
41. Segal ZV, Williams JMG, Teasdale JD. *Mindfulness-based cognitive therapy for depression: A new approach to preventing relapse*. Mindfulness-based cognitive therapy for depression: A new approach to preventing relapse. Guilford Press; 2002:xiv, 351-xiv, 351.
42. Schulz KP, Fan J, Magidina O, Marks DJ, Hahn B, Halperin JM. Does the emotional go/no-go task really measure behavioral inhibition? Convergence with measures on a non-emotional analog. *Arch Clin Neuropsychol*. Feb 2007;22(2):151-60. doi:10.1016/j.acn.2006.12.001
43. Shields SA, Mallory ME, Simon A. The Body Awareness Questionnaire: Reliability and validity. *Journal of Personality Assessment*. 1989;53:802-815. doi:10.1207/s15327752jpa5304_16
44. Forsberg S, Fitzpatrick KK, Darcy A, et al. Development and evaluation of a treatment fidelity instrument for family-based treatment of adolescent anorexia nervosa. *Int J Eat Disord*. Aug 20 2014;doi:10.1002/eat.22337
45. Peyser D, Sysko R, Schulz C, Hildebrandt T. Development and Validation of Adherence and Integrity Scale for Family Based Interoceptive Exposure. Icahn School of Medicine at Mount Sinai; 2020.
46. Horvath A, Greenberg, L. Development and validation of the Working Alliance Inventory. doi:10.1037/0022-0167.36.2.223. *Journal of Counseling Psychology*. 1989;36(2):223-233. doi:10.1037/0022-0167.36.2.223



47. Greco LA, Baer RA, Smith GT. Assessing mindfulness in children and adolescents: development and validation of the Child and Adolescent Mindfulness Measure (CAMM). *Psychol Assess*. Sep 2011;23(3):606-14. doi:10.1037/a0022819
48. National Cancer Institute. Dietary Screener Questionnaire in NHANES 2009–2010.
49. *nQuery*. Version 8.0. Statistical Solutions, Ltd; 2022.
50. Zahra D, Hedge C, Pesola F, Burr S. Accounting for test reliability in student progression: the reliable change index. *Med Educ*. Jul 2016;50(7):738-45. doi:10.1111/medu.13059
51. Scutari M. Bayesian Network Constraint-Based Structure Learning Algorithms: Parallel and Optimized Implementations in the bnlearn R Package. *Journal of Statistical Software*. 03/31 2017;77(2):1 - 20. doi:10.18637/jss.v077.i02
52. *Mixed Effects Dose Response Curves; medrc package*. 2017. <https://doseresponse.github.io/medrc/index.html>
53. Tang M, Slud EV, Pfeiffer RM. Goodness of Fit Tests for Linear Mixed Models. *J Multivar Anal*. Sep 2014;130:176-193. doi:10.1016/j.jmva.2014.03.012
54. Asparouhov T, Hamaker EL, Muthén B. Dynamic Structural Equation Models. *Structural Equation Modeling: A Multidisciplinary Journal*. 2018/05/04 2018;25(3):359-388. doi:10.1080/10705511.2017.1406803
55. D'Arcey TJ, M. Ennis, M. . Assessing the validity of FaceReader using facial electromyography. *Proceedings of APS 24th annual meeting*. 2012;
56. Leppanen J, Dapelo MM, Davies H, Lang K, Treasure J, Tchanturia K. Computerised analysis of facial emotion expression in eating disorders. *PLoS One*. 2017;12(6):e0178972. doi:10.1371/journal.pone.0178972
57. McNeish D, Hamaker EL. A primer on two-level dynamic structural equation models for intensive longitudinal data in Mplus. *Psychol Methods*. Oct 2020;25(5):610-635. doi:10.1037/met0000250
58. Scutari M, Denis J-B. *Bayesian Networks: With Examples in R*. Second Edition ed. Texts in Statistical Science. CRC Press; 2022.
59. Liu J, Zhou M, Wang S, Liu P. A comparative study of network robustness measures. *Frontiers of Computer Science*. 2017;11(4):568-584.
60. Steinglass J, Sysko R, Schebendach J, Broft A, Strober M, Walsh BT. The application of exposure therapy and D-cycloserine to the treatment of anorexia nervosa: a preliminary trial. *J Psychiatr Pract*. Jul 2007;13(4):238-45. doi:10.1097/01.pra.0000281484.89075.a8
61. Sysko R, Walsh BT, Schebendach J, Wilson GT. Eating behavior among women with anorexia nervosa. *The American journal of clinical nutrition*. Aug 2005;82(2):296-301. doi:82/2/296 [pii]

