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ABBREVIATIONS AND DEFINITIONS OF TERMS

AN		Anorexia Nervosa
AE		Adverse event
CRT		Cognitive Remediation Training
FBT		Family Behavioral Treatment
TBI		Traumatic Brain Injury
ICH		International Conference on Harmonization
CHOP		Children's Hospital of Philadelphia
PI		Principal Investigator
IQ		Intelligence Quotient
CRT_P		Parent-focused Cognitive Remediation Therapy
CRT_A		Adolescent-focused Cognitive Remediation Therapy
DSMB		Data Safety and Monitoring Board
EDATP		Eating Disorder Assessment and Treatment Program

ABSTRACT.

Context: (Background)
Anorexia nervosa (AN) is a severe psychiatric condition; the hallmark features are low body weight and difficulties gaining weight. Family based treatment (FBT) is the most effective treatment; however, only 50% of adolescents improve. Cognitive Remediation Therapy (CRT) may augment treatment and improve outcome. The best way to add CRT to FBT remains understudied.

Objectives: (primary and important secondary objectives)
The primary objectives include determining whether or not Cognitive Remediation Therapy (CRT) can increase set-shifting in parents and/or adolescents with Anorexia Nervosa (AN). The second objective is to determine the appropriate dose of CRT needed to achieve positive change in set-shifting.

Study Design:
Randomized controlled trial with three groups.

Setting/Participants:
Participants will be 60 adolescents with AN and their families. Treatment will occur on an outpatient basis at Children's Hospital of Philadelphia.

Study Interventions and Measures:
All adolescents with AN enrolled in the trial will receive FBT. Families will be randomized to FBT only, Family Based Treatment + Parent Focus Cognitive Remediation Therapy, or Family Based Treatment + Adolescent Focused Cognitive Remediation Therapy. Psychosocial, neurocognitive, and behavioral measures will be collected throughout the study.

TABLE 1: SCHEDULE OF STUDY PROCEDURES

Study Phase	**Screening**	**Treatment/Intervention**																		**3- and 6-month follow-ups and 12 optional FBT sessions**	
Visit Number		**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
Assessment		**1**				**2**					**3**				**4**					**5**	**6**	**7**
Informed Consent/Assent		X																				
Review Inclusion/ Exclusion Criteria	X	X																				
Medical Chart Review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height and Weight		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
2D:4D measurement		X																				
Treatment			X	X	X	X	X	X	X	X		X	X	X		X	X	X	X			
Questionnaire Battery																						
BRIEF-2[#]		X									X				X					X	X	X
ABOS[§]		X				X					X				X					X	X	X
AESED[§]		X				X					X				X					X	X	X
EDE-Q*		X				X					X				X					X	X	X

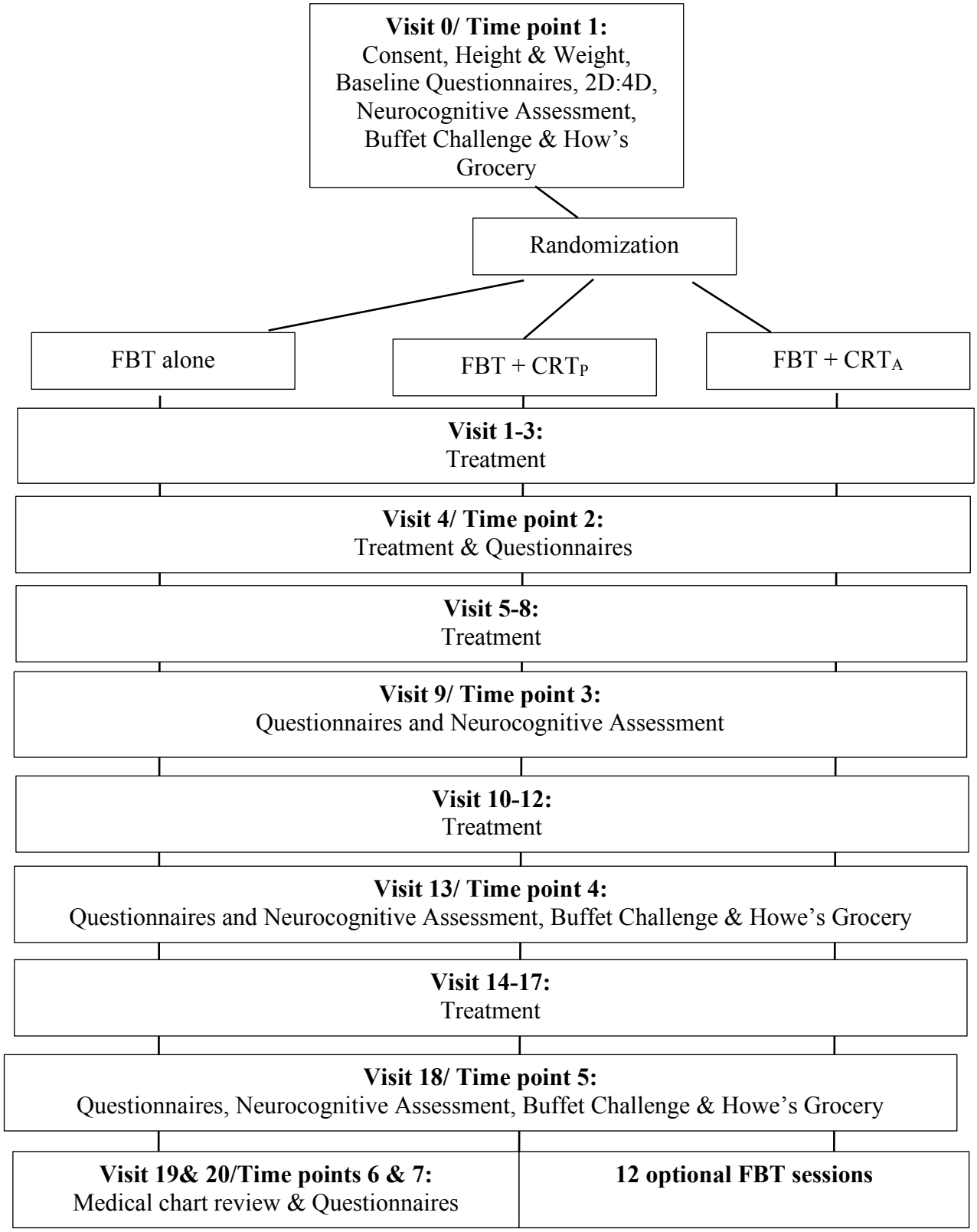
BIS/BAS[#]		X				X					X				X					X		
BASC-3[#]		X				X					X				X					X		
ECI[§]		X				X					X				X					X		
IUS[#]		X				X					X				X					X		
OCI[#]		X				X					X				X					X		
DFLEX[#]		X				X					X				X					X	X	X
FamQ[§]		X				X					X				X					X		
DASS[#]		X				X					X				X					X		
EDFLIX*		X				X					X				X						X	X
SRQ*		X				X					X				X							
AQ[#]		X				X					X				X							
CEQ[#]		X																				
WAI[∞]						X					X				X					X		
TEQ[#]																				X		
PVA		X				X					X				X					X	X	X
Neurocognitive Assessment																						
WASI[#]		X																		X *		
RCFT[#]		X									X				X					X		
DKEFS[#]		X									X				X					X		
LBT*		X									X				X					X		
Buffet Challenge*		X													X					X		
Howe's Grocery[§]		X													X					X		
AAT[#]		X				X					X				X					X		

§Parent only completes this measure
*Adolescent only

[#] Parents and Adolescent complete this measure
∞ Parent, adolescent, and therapist complete this measure

.

FIGURE 1: STUDY DIAGRAM



1 BACKGROUND INFORMATION AND RATIONALE

Anorexia Nervosa (AN) is a serious eating disorder characterized by restriction of food intake and reduction of body weight below what is healthy or expected for someone of the same age and height. AN has the highest mortality rate of all psychiatric disorders[1,2] and is associated with significant morbidity.[1] AN often begins during adolescence[3] and early intervention is key in order to prevent a chronic, unremitting course of the disorder.[4] To date, there is only one intervention with substantial empirical support for the treatment of AN in adolescents: Family Based Treatment.[5,6] In FBT, parents are essential to treatment and are charged with the task of re- nourishing their starving child. The effectiveness of FBT has established the importance of the family in treatment and empowered parents to play an active role in treatment.[7,8]

Studies in adults[9-12] and adolescents[13-16] with AN indicate that they have reduced behavioral flexibility (e.g., extreme perfectionism, perseveration, difficulties in learning new behaviors)[17] that reflects underlying neurocognitive inefficiencies, specifically set shifting.[18-20] Set-shifting is the ability to switch tasks, change mindsets, rapidly adapt to new situations, and respond to new environmental contingencies.[21] The evidence of set-shifting difficulties in adults with AN is robust enough that it is considered a putative endophenotype.[18,22] Endophenotypes are intermediate phenotypes that must be associated with an illness, be present within the individual regardless of the state of the illness, and are inherited. They are found in family members of the proband at a higher rate than in the population and within the family the illness and endophenotype are inherited together (co-segregate).[23] Set-shifting inefficiencies in AN do not fully improve with re-nourishment.[24] Similar inefficiencies are found in siblings and parents of individuals with AN.[18,25-27] Executive functioning is heritable[28] and there is preliminary evidence of co-segregation of cognitive inefficiencies in the context of AN.[26] If set-shifting difficulties are an endophenotype - parents of adolescents with AN have a greater likelihood of having cognitive inefficiencies that may be exacerbated by the stress of caring for an ill child. Increased difficulties in set-shifting could lead to greater difficulty implementing FBT at home and poorer or less rapid gains for their child. Cognitive Remediation Therapy (CRT) is an adjunctive treatment that improves cognitive flexibility and can be used with the parents or child.

Via structured input and repetition, CRT leverages the brain's natural neuroplasticity and fosters changes in brain structure and connections. CRT can be restorative (focusing on decreasing cognitive inefficiencies), compensatory (maximize daily functioning without changing cognitive impairments), or metacognitive (monitoring one's own thinking and subsequently adapting behavior to the environment).[29] CRT for AN is metacognitive. The goal of CRT is to target a cognitive inefficiency using principles of learning in order to improve functional outcomes (i.e., improving memory in traumatic brain injury (TBI) significantly improves the probability of a return to work).[30-32] CRT has a long history of improving aspects of executive functioning leading to positive impacts on behavior across a number of conditions (including, TBI[33] depression,[31,34] schizophrenia,[35,36] and eating disorders[37,38]). Recent work in AN indicates that CRT can improve eating disorder quality of life and may have a positive impact on weight gain.[39,40] CRT addresses many characteristics of adolescents with AN that can make treatment more difficult.

CRT for AN has an unambiguous target: cognitive flexibility. By improving this important aspect of a broader system, treatment gains can be maximized. Augmenting treatment with CRT

can potentially strengthen inherited inefficiencies and/or prevent the worsening of neurocognitive abilities due to prolonged malnourishment. Alternatively, as parents are the primary implementers of treatment, targeting their cognitive flexibility can increase their ability to (behaviorally) flexibly respond to contingencies in the environment and implement behavioral plans with their sick child. In turn, parents may be able restore their child's weight more quickly and with a diet that is more macronutrient varied. Increasing flexibility in either the parent or child can impact a larger system of behaviors and lead to improved clinical outcome, including more a macronutrient varied diet and subsequent increase in rate of weight gain.

1.1 Introduction

Augmenting FBT with CRT has the potential to impact the rate at which adolescents gain weight. While the vast majority of research has focused on CRT for adolescents, we propose that it may be more impactful to target the adolescent with AN's parents as parents are the individuals carrying the burden of treatment and re-nourishment of their child. Parent only modifications of FBT are effective in increasing weight in adolescents with AN,[41-43] thus a parent focused intervention can be effective.

The purpose of this project is to establish that CRT can move the target of flexibility. The goal is to determine whether or not flexibility improves more in the parent or the adolescent and what dose of CRT is needed to achieve gains in flexibility.

1.2 Name and Description of Investigational Product or Intervention

1.2.1 Family Based Treatment (FBT)

FBT is a manualized family treatment for adolescents with AN. It is effective for children and adolescents aged 12-18. It is a conjoint family treatment with all family members attending all sessions. For this study, we will use a 15 session version of FBT used in prior research. The goal of treatment is weight restoration and reduction of eating disorder symptoms. The primary focus of treatment sessions is to activate and empower the parents of the affected child to restore weight. Secondary goals of FBT include aligning the parental and sibling subsystems and reestablishing healthy adolescent developmental trajectories. Treatment will occur weekly at the beginning of treatment, move to bi-weekly, and then monthly for the last month of treatment. Families will have the option of receiving 12 additional FBT sessions after completing the first 15 sessions. These 12 sessions will be scheduled as families see fit and will occur over the course of six months.

The treatment takes place over 3 phases:

1. Refeeding and Weight Restoration
2. Returning Control of Eating to the Adolescent
3. Addressing Adolescent Issues and Treatment Completion

The PI has received training in the manual and has recently completed the necessary hours for certification in this treatment modality.

1.2.2 Cognitive Remediation Therapy

CRT is an adjunctive intervention focusing on the development of meta-cognition – teaching individuals to think about how they think.[44] It involves presenting individuals with a variety of

tasks requiring increasingly complex mental abilities – these include geometric figures, illusions, reversing sequences of numbers and letters, completing sorting tasks wherein the rules change, and finding various routes on a map.[45] Most importantly, CRT focuses on process instead of outcome. That is, instead of focusing on whether or not a task was accurately completed, individuals in CRT are asked to think about how they solved a puzzle, reflect on their thought processes, and identify steps in problem solving. CRT has three goals:

1. Improve brain function by exercising and increasing connections in the brain
2. Encourage individuals to think about their thinking style
3. Encourage individuals and families to spend time away from thinking about the eating disorder.

CRT can be delivered in individual, family, and group formats.[46-48] For this study, we will administer CRT to either adolescents or their parents. CRT will be delivered for 45-60 minutes prior to FBT sessions for a total of 15 sessions. Participants in CRT will be given weekly homework.

1.3 Relevant Literature and Data

Anorexia Nervosa (AN) is a life-threatening disorder with a significant impact on the quality of life of those afflicted. Age of onset is typically during adolescence; it significantly alters patterns of healthy growth and development in adolescents and can impact the functioning of the entire family. Severe starvation during the critical period of adolescence affects all developing systems, especially brain development. Results from longitudinal studies of brain function in adults with AN indicate that sufferers have long term difficulties with executive functioning and demonstrate behavioral rigidity (e.g., perseveration, extreme perfectionism, difficulties in learning new behaviors) that reflects underlying neuro-cognitive deficits.[18,49] These underlying difficulties in executive functioning could be indicative of underlying traits that create of vulnerably to developing AN, they could be the result of starvation during a critical period, or they could be a marker for those who are likely to have a more chronic course of the disorder. Regardless as to whether or not they are a cause or consequence of AN, it is likely that behaviors associated with neurocognitive deficits can maintain AN or interfere with treatment. Thus, addressing executive functioning, specifically that related to flexibility may have a positive impact on treatment outcome. Cognitive Remediation Therapy for AN was developed to do just that.

Evidence for CRT in adolescents. CRT has been successfully developed for adolescents and for administration during a hospital stay.[50] CRT has been proposed as a viable pre-intervention or adjunct to other forms of treatment.[39] It increases cognitive flexibility in adult and adolescent patients with AN.[38,51,52] For adolescents with AN, CRT is generally well received and can result in increased motivation to engage in treatment.[52] Parents report feeling as if the rationale for CRT helps them understand their child's behavioral difficulties.[50] A family-based form of CRT for adolescents with AN facilitated parents' ability to recognize their own and their child's thinking style and helped the family to develop strategies to cope with these thinking styles.[52] CRT is generally well received by patients and parents, may increase treatment retention, and has a demonstrated impact on executive functioning.[44] Despite preliminary positive findings, research on CRT in adolescents is limited.[38] The dearth of research in this area is a significant gap in our knowledge regarding how best to apply CRT.

Augmenting FBT with *CRT for parents* may impact weight more. Inefficiencies in cognitive flexibility are likely inherited; thus, it is reasonable to assume that parents may also struggle with flexibility. Prolonged stress (such as having a child with a potentially lethal illness) can decrease flexibility and narrow behavioral repertoires in face of threat.[53-55] Parents who have cognitive inefficiencies in the area of set shifting *and* who are tasked with caring for an acutely ill child may struggle with being flexible in the moment. If parents of an adolescent with AN do not have cognitive inefficiencies, they likely experience a state-based reduction in flexibility. Whether state, trait, or combination of both – difficulties in cognitive and behavioral flexibility can translate into more difficulties implementing exposure to symptom specific stimuli and greater symptom accommodation which leads to less macronutrient variation and a slower rate of weight gain. Given that parental control of eating is a strong predictor of weight gain,[56] augmenting treatment with CRT to maximize their ability to do so has the potential to increase the number of adolescents who reach remission.

The purpose of this study is to further investigate the role of CRT in the treatment of adolescent AN. The goal of this study is to determine whether or CRT increases flexibility in adolescents or parents, if this increase is more than what is observed in FBT alone, and what the dose of CRT is needed to increase flexibility.

1.4 Compliance Statement

This study will be conducted in full accordance all applicable Children's Hospital of Philadelphia Research Policies and Procedures and all applicable Federal and state laws and regulations including 45 CFR 46, and the Good Clinical Practice: Consolidated Guideline approved by the International Conference on Harmonization (ICH). All episodes of noncompliance will be documented.

The investigators will perform the study in accordance with this protocol, will obtain consent and assent, and will report unanticipated problems involving risks to subjects or others in accordance with The Children's Hospital of Philadelphia IRB Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

2 STUDY OBJECTIVES

The purpose of the study is to determine whether or not augmenting FBT with CRT for parents or adolescents significantly improves cognitive flexibility and the dose required to do so.

2.1 Primary Objective (or Aim)

Aim 1: To identify whether or not it more impactful to add a parent or adolescent component of CRT to standard FBT. We hypothesize that both adolescents and parents who receive CRT will have greater increases in cognitive flexibility than those who receive FBT alone. We will examine magnitude of change in cognitive flexibility across groups.

Aim 2: To determine the dose of CRT needed to lead to a medium effect size (increase in cognitive flexibility). We will examine the dose of CRT needed to obtain an increase in cognitive flexibility equal to a medium effect.

2.2 Secondary Objectives (or Aim)

- Collect preliminary data on outcome

3 INVESTIGATIONAL PLAN

3.1 General Schema of Study Design

3.1.1 Screening Phase

Potential participants will be identified during presentation for treatment at CHOP for an eating disorder. This includes during initial hospitalization for medical stabilization, during outpatient intake assessment, or during the initial medical visit and evaluation. Additionally, potential participants may respond to flyers and tearpads, and independently demonstrate interest in participating by getting in touch with the research coordinators. A member of the study staff will administer a verbal screening over the phone to determine adolescent and parent eligibility. All potential participants who appear to meet inclusion will be provided with information about the clinical trial along with other treatment options. Families who are interested will meet with the study coordinator or research assistants, be provided with more information, and (if inclusion and exclusion criteria are met) scheduled for an intake.
Parental/guardian permission (informed consent) will be obtained prior to any study procedures taking place.

3.1.2 Study Intake

The intake appointment is comprehensive and typically lasts an entire day. The intake battery being used is comparable to one used in other studies by the PI with no ill effects. Families are informed of the length of the intake prior to arrival and it has been well tolerated in the past.

The intake begins with informed consent. Once consent is received, every effort will be made to ensure the family will complete all aspects of the baseline assessment (see Table 1).

Parents and the adolescent will complete a standard questionnaire battery, neuro-psychological assessment, IQ assessment, and a number of behavioral tasks. In addition, the adolescents will complete a diagnostic interview to assess eating disorder symptoms. As part of the intake, the adolescent will be asked to serve and eat a meal. This will be videotaped.

Video-taping will be done using a CHOP approved device. Data will be uploaded to the CHOP server and deleted from the device. All videos will be retained for 6 years and destroyed at that time.

At the end of the intake, the family will meet with their therapist, who will complete the clinical interview and provide information for and schedule the next session. Randomization occurs after the clinical interview.

Consent and assessments will ideally occur in-person; however, if this is not possible then remote consent and assessment will occur. Remote consent will take place on a CHOP-approved video conferencing platform, and study staff will review all sections of the informed consent form with families. Families will be sent a link to our REDCap project with the informed consent form. At the end of the informed consent discussion, families will be asked to e-sign and e-date

in the appropriate sections of the REDCap project. An electronic copy of the informed consent form will also be sent to the families for their records, and a signed version of the informed consent form will be available on REDCap for families to download. Remote assessments will also take place via CHOP-approved video conferencing platforms and will involve all tasks that do not involve physical manipulation of objects and will also not include the buffet challenge. If visits are done remotely, we may ask the parents to weigh their child and share this weight with the study therapist or assessor.

3.1.3 Study Treatment Phase (start of the study intervention)

After the baseline assessment/intake, the family will be randomized to one of three conditions: Family Based Treatment (FBT), Parent Focused Cognitive Remediation Therapy + FBT (CRT_P), or Adolescent Focused Cognitive Remediation Therapy + FBT (CRT_A). Families will have 15 sessions of the assigned treatment and be assessed at 4 additional time points (baseline intake + 4 more is a total of 5 time points). For treatment, all standard clinical procedures will be followed.

In the event of an unforeseen circumstance whereby one's presence at CHOP puts the patient, family, and/or CHOP staff at risk, treatment sessions can be done remotely. All treatment sessions done remotely will take place on a CHOP-approved video conferencing app, such as Vidyo or Skype Business. If treatment sessions are done remotely, we may ask the family to weigh their child and share this weight with the study therapist. A note to file is being made for every treatment session that occurs remotely and will be reported to the IRB and DSMB in a yearly report.

3.1.4 Assessments

Assessments will occur at baseline and then 4 additional times during treatment (total of 5) according to the schedule outlined in Table 1. Assessments will be scheduled within a week of the therapy appointment, ideally on the same day to minimize burden on the family. Questionnaires can be completed on line prior to coming in for the assessment.

In the event of an unforeseen circumstance whereby one's presence at CHOP puts the patient, family, and/or CHOP staff at risk, assessments can be done remotely. All assessment sessions done remotely will take place on a CHOP-approved video conferencing app, such as Vidyo or Skype Business. Remote assessments will involve all tasks that do not involve physical manipulation of objects and will also not include the buffet challenge. If assessments are done remotely, we may ask the family to weigh their child and share this weight with the assessor. A note to file is being made for every assessment that occurs remotely and will be reported to the IRB and DSMB in a yearly report.

3.1.5 End of Treatment Evaluation

The End of Treatment Evaluation will occur within 14 days of treatment end. It will mirror the intake and include the measures noted in Table 1.

3.1.6 Post Treatment Follow-up

After finishing the study, participants will receive questionnaires via link in email (for RedCap) and/or paper versions mailed to them. These will be sent approximately 3- and 6-months after completing the study. Families will also have the option to receive an additional 12 FBT sessions during this time. The study team will also complete medical chart reviews during these two follow-up periods. Should an adolescent turn 18 years of age during post treatment follow-up, the study team will request that the adolescent makes an appointment for reconsenting after turning 18. This appointment can take place at any CHOP affiliated facility (e.g., Roberts Center for Pediatric Research, Adolescent Medicine Specialty Care Center, etc). If the adolescent is unable or unwilling to reconsent, they will not be sent questionnaires for completion. Parents, however, will be sent questionnaires.

3.2 Allocation to Treatment Groups and Blinding

The study statistician will facilitate the sequential randomization of participants employing a covariate-adaptive randomization method (using open source free software; OxMaR)[57] that ensures an equal distribution of males across the three conditions.[58,59] Minimization works by re-calculating the probability of allocation to the treatment and control groups after each new participant enters the cohort. The probability of assignment will depend on stratification by sex and age to assure that males have an equal probability of assignment to the different conditions, something that is not guaranteed with simple random assignment. The algorithms for doing this will be programmed ahead of time, study team members will enter the sex and age of participant into the program in order randomize them to groups. The statistician will not have access to any PHI.

Research assistants conducting assessments will be blinded to treatment condition at all time points.

3.3 Study Duration, Enrollment and Number of Sites

3.3.1 Duration of Study Participation

Total study duration for each participant is approximately 12-14 months. Participants will have 6-12 months of active treatment. If there is a delay in treatment (brief hospitalization or cancelation of an appointment due to weather, illness, etc.) treatment duration may be slightly longer. It is anticipated that all treatment will be complete within 12-14 months of enrollment.

Adolescents and their families will be assessed at five time points:

- T_1: neuropsychological assessment, therapy session, questionnaires, Grocery store (parents), Buffet challenge (adolescent)
- T_2: therapy session, questionnaires
- T_3: neuropsychological assessment, questionnaires
- T_4: neuropsychological assessment, questionnaires, Grocery store (parents), Buffet challenge (adolescent)
- T_5: questionnaires, neuropsychological assessment, Grocery store (parents), Buffet challenge (adolescent)

- T_6: Medical chart review and questionnaires (to be completed online/ mailed to the family, this will take place 3 months post end of primary treatment intervention)
- T_7: Medical chart review and questionnaires (to be completed online/ mailed to the family, this will take place 6 months post end of primary treatment intervention)

3.3.2 Total Number of Study Sites/Total Number of Subjects Projected

The study will only be conducted at Children's Hospital of Philadelphia.

It is expected that approximately 60 subjects will be enrolled to produce at least 45 evaluable subjects.

3.4 Study Population

3.4.1 Inclusion Criteria (Adolescent)

1. Age 12-18
2. Currently meets DSM-5 criteria for Anorexia Nervosa
3. Medically stable for outpatient treatment
4. Fluent in English
5. No co-morbid condition that would exclude participation (diagnosis of a pervasive developmental disability or mental retardation, psychosis, bipolar disorder, substance abuse, or autism spectrum disorder)
6. Medical clearance from primary care physician and permission to speak to PCP about clinical issues
7. Biological parents or primary caregivers willing to engage in treatment and who live with the adolescent.

3.4.2 Inclusion Criteria (Parents)

1 Age >18
2. Child with a diagnosis of AN
3. Both parents willing to participate
4. Fluent in English
5. No co-morbid condition that would exclude participation

3.4.3 Exclusion Criteria (Adolescent)

1. Outside of age range
2. Adopted
3. No more than four sessions of prior CRT in any format
4. Presence of: pervasive developmental disability, psychosis, bipolar disorder, substance abuse, autism spectrum disorder, or intellectual disability.
5. Presence of: a brain disorder or injury (such as TBI) that could impact the ability to engage in treatment
6. Use of anti-psychotic medication during first 15 FBT sessions. Use of this medication is permitted in the optional 12 FBT sessions in the 6-month follow-up period of this study. This medication can affect cognitive abilities, which may interact with assessments that measure cognitive flexibility. However, we do not measure cognitive flexibility in the 6-month follow-up period when the 12 additional FBT sessions can take place.

7. Concurrent psychosocial therapy

3.4.4 Exclusion Criteria (Parents)

1. Presence of: pervasive developmental disability, psychosis, bipolar disorder, substance abuse, autism spectrum disorder, or intellectual disability.
2. Presence of: a brain disorder or injury (such as TBI) that could impact the ability to engage in treatment
3. Use of anti-psychotic medication during first 15 FBT sessions. Use of this medication is permitted in the optional 12 FBT sessions in the 6-month follow-up period of this study. This medication can affect cognitive abilities, which may interact with assessments that measure cognitive flexibility. However, we do not measure cognitive flexibility in the 6-month follow-up period when the 12 additional FBT sessions can take place.
4. No more than four sessions of prior CRT in any format

Subjects who do not meet all of the enrollment criteria will not be enrolled. Any violations of these criteria will be reported in accordance with IRB Policies and Procedures.
Patients with AN who receive psychosocial treatment at CHOP are typically followed by adolescent medicine at CHOP. Though it is possible that an adolescent will enter the trial and not be followed by CHOP's adolescent medicine, this is extremely unlikely. If it does happen, the adolescent will need to be followed by his or her pediatrician for the duration of the study and permission to speak to the pediatrician will be obtained (standard of care).

Concurrent psychosocial therapy for the adolescent is an exclusionary criterion. Given the life-threatening nature of AN, treatment for it is primary. It is standard of care for the outpatient program at CHOP to request that patients discontinue with outside therapy while receiving treatment for the eating disorder. In addition to eliminating any confounding effects of outside treatment, this practice follows the current standard of care and will be used in this study. If medication is prescribed for the adolescent it is typically done by either adolescent medicine, the adolescent's primary pediatrician, or by CHOP psychiatry. Visits with psychiatry (either within or outside of CHOP) will be allowed for medication management only. Any changes in medication will be confirmed with the prescribing physician or through the medical chart (if at CHOP) and noted.

4 STUDY PROCEDURES

4.1 Study Intake (Visit 0)

- Informed Consent
- Medical Record Review (without participants)
- Height and weight
- Questionnaires
- Buffet Challenge
- Howe's Grocery
- Neuropsychological and IQ testing
- 2D:4D measurement
- Clinical interview (video recorded)
- Treatment sessions (audio or video recorded)

4.2 Study Treatment Phase

General overview of this phase.

4.2.1 Visit 1-8, 10-12, 14-17

Each visit the family will receive the treatment assigned during randomization (FBT, CRT_P, or CRT_A). The following will happen at each session:

- Height and weight
- Review of homework
- Study intervention
- Medical Record Review (without participants)

4.2.2 Visit 4

- Questionnaires (online or in-person)
- Height and weight
- Medical Record Review (without participants)

4.2.3 Visit 9

- Medical Record Review (without participants)
- Height and weight
- Questionnaires (online or in-person)
- Neuropsychological testing

4.2.4 Visit 13

- Medical Record Review (without participants)
- Height and weight
- Questionnaires (online or in-person)
- Buffet Challenge
- Howe's Grocery
- Neuropsychological testing

4.2.5 End of treatment evaluation (Visit 18)

- Medical Record Review (without participants)
- Questionnaires (online or in-person)
- Height and Weight
- Buffet Challenge
- Howe's Grocery
- Neuropsychological and IQ testing
- Clinical interview

4.2.6 Optional continuation of FBT

- 12 optional additional sessions of FBT

4.2.7 Visits 19 and 20

- Medical Chart Review (without participants)
- Questionnaires (online or by mail)

4.3 Permission to Speak with Physician

Appropriate **clinical** management of AN requires that the treatment team be in communication. Participants must provide consent for the study therapist to speak with the medical provider to coordinate care (e.g., the therapist will need to know when the adolescent is medically able to return to school, exercise, or sports). In order for this clinical coordination to occur, the physician **does not** have to be informed of the participant's participation in a clinical trial. Whether or not the physician is informed of study participation is at the participant's participants' discretion. As the primary treatment provided in this study is FBT and standard of care, there is no reason to expect the physician to think the adolescent is participating in a study.

4.4 Unscheduled Visits

Unscheduled visits will not be permitted. Contact with families between sessions will be as needed or on an emergent basis. Contact will be documented and must be in line with the appropriate treatment.

4.5 Concomitant Medication

All prior and concomitant medications used within 30 days prior to the screening visit and through the end of the study will be recorded. The dates of administration, dosage, and reason for use will be included.

4.6 Hospitalization during Treatment

Adolescents will be followed by their medical doctor during treatment; this is usually adolescent medicine at CHOP. Should the medical doctor determine that the adolescent needs to be hospitalized for medical stabilization, this recommendation will be followed. Adolescents will be allowed to return to the trial post-hospitalization. Eating disorder symptomatology and weight will be assessed post-discharge from hospital. Any medication changes/additions will be noted. If, however, the adolescent needs to be referred to a higher level of care (e.g., inpatient treatment), then the adolescent will be removed from treatment in the trial.

4.7 Subject Completion/Withdrawal

Subjects may withdraw from the study at any time without prejudice to their care. They may also be discontinued from the study at the discretion of the Investigator for lack of adherence to study treatment or visit schedules, AEs, or due to need to refer to a higher level of care (inpatient or residential treatment). The Investigator may also withdraw subjects who violate the study plan, or to protect the subject for reasons of safety or for administrative reasons. It will be documented whether or not each subject completes the clinical study. If the Investigator becomes aware of any serious, related adverse events after the subject completes or withdraws from the study, they will be recorded in the source documents and on the case report form.

4.8 Early Termination Study Visit

Subjects who withdraw from the study will be asked complete the full questionnaire battery. Should the family not wish to complete these measures, data from their last visit will serve as the last data point.

5 STUDY EVALUATIONS AND MEASUREMENTS

5.1 Screening and Monitoring Evaluations and Measurements

5.1.1 Medical Record Review

Include a listing of the variables that will be abstracted from the medical chart (paper or electronic).

- Date of birth
- Height
- Lowest weight
- Highest weight
- DSM-5 criteria for Anorexia Nervosa
- Expected body weight (i.e., target goal weight for weight restoration)
- Expected height (for those who have lost linear height)
- Date of last menstrual period (if menarche has begun)
- Parental date of birth (necessary for neuropsychological assessment)
- Race (parental and adolescent)
- Ethnicity (parental and adolescent)
- Familial history of eating disorders
- Parental height and weight
- Mid-parental height
- Hormonal levels
- Vitals
- Daily Weight
- Caloric Intake
- Medication

5.1.2 Other Evaluations, Measures

We will collect demographic information from the adolescent and parents. This includes age, date of birth, sex, race/ethnic.

5.1.2.1 Cognitive flexibility

Wechsler Abbreviated Scale of Intelligence (WASI;[60]): The WASI is a nationally standardized measure of general intellectual functioning used in clinical, educational, and research settings that scores individuals on four subtests: Vocabulary, Similarities, Block Design, and Matrix Reasoning. We will administer the two subscale version of the WASI to calculate IQ. This is necessary to provide a context in which to understand the results of the neuro-psychological testing.

Rey-Osterrieth Complex Figure Test (RCFT;[61]): The RCFT measures visual-spatial perception, construction, non-verbal memory, planning, problem solving, and motor function. This test is pen and paper based requiring participants to copy a complex figure. There are two important components to the recreation of the complex figure: recalling it after a brief period of time without priming and the copying it. It is valid to use in adolescents with AN.[62] It is used as a measure of central coherence. Central coherence has been demonstrated to be impaired in some adolescents with AN.

Delis-Kaplan Executive Functioning Scales (DKEFS;[63]). The DKEFS is a comprehensive, standardized battery of assessments of executive functioning that can be used with children and adults, ages 8–89 years. It has also been validated for use with adolescents with AN.[64] Selected subtests administered included: trail making test, verbal fluency test, color-word interference test, and sorting test.

Behavior Rating Inventory of Executive Function-2 (BRIEF-2;[65]). The BRIEF-2 is an 86 item questionnaire that assesses executive functioning in children and adolescents aged 5 to 18 years of age. There is a global executive composite score as well as subordinate indices examining behavioral regulation and metacognition. The Behavioral Regulation index consists of subscales measuring inhibition, set-shifting, and emotional control. The Metacognition index consists of subscales looking at initiate, working memory, planning and organizing, organization of materials, and monitoring one's own work. Internal reliability has been found to be good with an alpha of .96 for the Behavioral Regulation Index and an alpha of .96 for the Metacognition index. Adolescents will complete this about themselves and parents will complete it about the adolescent and themselves.

5.1.2.2 Weight and Eating Disorder Symptoms

Anorectic Behavior Observation Scale (ABOS;[66]). This 30-item self-report measure taps into parents' observations of their child's disordered eating behavior. This measure has good specificity (89.6%) and sensitivity (90%) in terms of parental report of ED symptoms; and it is correlated with other measures of disordered eating behavior. There are three subscales in this measure: eating behavior (α=0.80), bulimic-like behavior (α=0.69), and hyperactivity (α=0.69). Good internal consistency has been found for each subscale. This measure is completed by parents and corroborates adolescent report of sympotms.

Accommodation and Enabling Scale for Eating Disorders-Revised (AESED;[67,68]). This 41-item measure gathers information about the enabling behaviors that family members with a child who has an eating disorder engage in. It is a revised version of a measure developed for use with adults. The origional measure contains three subscales: avoidance and modifying routine, meal ritual, and control of the family. The origional scale has internal consistency values ranging from 0.77 to 0.92. Only parents complete this measure.

Eating Disorder Examination – Querstionnaire (EDE-Q;[71, 72]). The EDE-Q is a 29-item questionnaire that is a self-report version of the Eating Disorder Examination (EDE). We use a self-report measure to reduce participant burden yet allow for assessment at specific time points. This measure assesses four symptom domains : restraint (α=0.75), eating (α=0.78), weight (α=0.67), and shape concerns (α=0.79) as well as the presence and severity of specific ED behaviors. This will be used to establish diagnosis and remission status. To track change over treatment and follow-up, the 28 item self-report version of the EDE will be used. Finally, to track weekly change and assess any changes in eating disorder sympotmatology that might occur during medical hosptializaiton, a 12 item brief version of the EDE will be used. The EDE and its variants are the gold-standard in symptom assessment for eating disorders.

5.1.2.3 Behavioral Flexibility

Howe's grocery. Howe's grocery is a website that mimics an online grocery store. The store contains 8000 products across various categories (e.g., breads, produce, beverages, snack foods). Each product is an actual product with the exception of store brand "Howe's" products. Product nutrition information and price are accurate as of February 2018. By clicking "check out" consumers indicate they have finished their shopping trip. Consumers are not charged for and they do not receive any groceries. Howe's grocery has a logging framework that allows researchers have a granularity of understanding where users click, spend the most time, or the sequence of additions and removals from the user's cart. In this study, parents' food choices in their cart can be analyzed for macronutrient and caloric content. Parents will be asked to do three days of meal planning and then "shop" for those menu items on-line.

Buffet Challenge. Adolescents with AN will be presented with a buffet of food options (See Table 2). Buffet options were created in collaboration with a nutritionist and generated from items in the Food Choice Task.[73] We chose to present adolescents with actual food items instead of a computerized task as there may be a difference between being able to choose more varied food on a computer and actually choosing and consuming foods. Food options will include both "safe" foods (such as salad, lean protein) and common "fear" foods (pasta, pizza, desserts). Adolescents will approach the buffet, serve food, and consume the meal without coaching or support from parents. The meal will be videotaped and the following data collected: time to approach buffet, time spent serving food, time eating food, amount of food chosen (weight and calories), macronutrient profile of food chosen, and amount (calories and macronutrients) eaten. We will also code for meal time behaviors reported in Gianini[74] (e.g., tearing, staring, dissecting).

Approach-Avoidance Task (AAT): The AAT assesses approach-avoidance tendencies. Single stimuli are presented to participants on a computer screen. In response to the images, the participant presses a computer key. One key represents a positive valence, or an "approach" response, and the other represents a negative valence, or an "avoidant" response. Unique deduction of stimuli valence, which, for this study, will display as food items. With a keyboard, participants will press one of two buttons for each stimulus presented to them. The images displayed in this AAT will be that of food items (e.g., pizza and cake) or personal care items (e.g., toothbrush or towel).

Table 2. Buffet Challenge Foods (sample)

grilled chicken	yogurt and granola
tofu	salad bar
doughnuts/brownies	wrap/sandwich bar
French fries	chocolate
chicken fingers	mac and cheese
veggies	plain pasta with
peanut or almond	red sauce
butter	pizza

5.1.2.4 Comorbid symptoms and potential moderators

Behavioral Inhibition System and Behavioral Activation System Scales (BIS/BAS;[75]). The behavioral inhibition system (BIS) and behavioral activation system (BAS) scales are self-report measures used to examine a patient's inhibition and activation sensitivity. The scale is composed of four sub scales, one scale to measure BIS sensitivity, and three subscales related to BAS sensitivity (Drive, Fun Seeking, and Reward Responsiveness Scales). The BIS component measures patient sensitivity to signals of punishment, for example, patients high in BIS sensitivity are more responsive to punishment cues and experience greater negative affect (anxiety) in situations associated with punishment. The BAS component measures sensitivity to signals of reward, for example, patients with high BAS sensitivity are highly responsive to reward cues and experience positive affect. Internal consistency was high for the BIS (α=0.74), BASS Reward Responsiveness (α=0.73), BAS Drive (α=0.76), and BAS Fun Seeking (α=0.66). Recently, AN has been hypothesized to be related to abnormalities in reward processing. Adolescents will complete this about themselves; parents will complete it about themselves and their child.

Behavior Assessment System for Children-3 Parent and Child Version (BASC-3;[76]). This is 139 item self-report measure that assesses affective and behavioral functioning in adolescents. The BASC-3 is well validated and has reliability ranging from .88-.97 with test-retest reliability of .81-.89. Both parent and self-report versions are available, allowing for comparison of parent and self observations of behavior. The measure includes both adaptive scales (e.g. Daily Living, Social Skills, Functional Communication) and clinical scales (e.g. Depression, Anxiety, Withdrawal, Atypically). Given that mood disorders and interpersonal deficits often accompany AN, a full assessment of these domains will allow broader based evaluation of treatment. It might also provide information regarding the adolescent's strengths and allow for tracking of improvement in adaptive areas.

Experience of Caregiving Inventory (ECI;[77]). This 66-item self-report measure assesses caregivers' perception of their experiences interacting with their child. It includes subscales with both negative (eight subscales) and positive items (two subscales). This measure is included to assess change in parental experience of having an ill child (i.e. greater hope for positive outcome, less judgmental of the adolescent). The ECI has demonstrated good construct validity (explaining 36% of the variance in scores on measures assessing general health and coping) and high internal consistency (Cronbach's alphas ranging from 0.74 to 0.91) among caregivers for patients with AN.[69] It is only completed by parents.

Intolerance of Uncertainty (IUS;[78]). The IUS is a 27 item self-report measure that assesses six aspects of intolerance to uncertainity, 1) the emotional and behavioral consequences of being uncertain, 2) how being uncetain relects on an individuals character, 3) expectations that the future be predictable, 4) frusteration surrounding unpredictability of the future, 5) attempts to control the future, 6) and all or nothing situations when in unceratin situations. Items are measured on a 5 point Likert scale. The IUS showed strong internal consistency (α = .94) and good test-retest reliablity (r =.74) over a 5 week period. The IUS is validated and considered to have good concurrent validity with measures of worry, anxiety, and depression. The IUS will be administered at all time points.

Obsessive Compulsive Inventory (OCI;[79]). There is an adult (OCI) and child (C-FOCI) version of this measure. The C-FOCI is a 17 item self-report questionnaire that assesses presence of common obsessions and compulsions. There are two parts to this scale – a symptom checklist and a severity scale. The adolescent checks yes or no for the checklist and for the scale endorse items according to a range from 0 (none) to 4 (extreme). The internal consistency was acceptable for both parts ranging from .76-.79. OCD is highly comorbid with AN and can appear as rigid behavior. Parents will complete the OCI about themselves. This is an 18 item scale using a 5 point Likert type response that assesses distress associated with obsessions and compulsions. It has good internal consistency reliability (.81-.93). Parents will complete the OCI.

Detail and Flexibility Questionnaire (DFlex;[80]). The DFlex is a 24-item self report measure assessing cognitive rigidity and attention to detail, both considered aspects of neurocognitive functioning. Both aspects have been measured in an Austistic sample using the Autism Spectrum Quotient (AQ), and thus the AQ was used to determine construct validity. A strong correlation for cognitive rigidity was shown (r = .72) and a moderate correlation for attention to detail (r = .26). The DFlex is a new measure developed to address both flexibility and central coherence. It will be completed by parents and adolescents.

Line Bisection Task (LBT;[81]). The LBT has been widely used as a behavioral measure of visual neglect in patients with brain damage. More recently, neuroimaging research has confirmed it can also be used to measure approach motivation in non-clinical populations. In the task participants mark the perceived mid-point of staggered horizontal lines of the same length in millimeters (mm). When participants make errors in marking the midpoint left of the true midpoint these are scored as negative. Meanwhile, positive scores mean greater left to right hemisphere activation. The LBT is being piloted in this study as a behavioral measure of approach-based coping. It will be completed by both adolescent and parents.

Family Questionnaire (FamQ;[82]). Expressed emotion (EE) has traditionally been assessed via clinical interview, however the interview can be laborious and time consuming. In order to address this issue, the FQ was developed. It is a 20 item self-report measure that includes two subscales: criticism and emotional over involvement. Scores on the FQ have high convergent validity with more traditional interview assessments of EE. Test-retest reliability over two weeks produced Pearsons correlations of r= 0.84 for the criticism (CC) and r=0.91 for the emotional overinvolvement (EOI) subscales. Similarly, internal consistency was good, ranging from 0.90-0.92 for the CC and 0.79-0.82 for the EOI subscales. Only parents will complete this measure.

Depression Anxiety Stress Scale (DASS;[83]): The DASS is a 42-item self-report instrument measuring current symptoms of depression, anxiety, and stress on three separate scales. Higher scores on each of the scales indicate higher levels of depression, anxiety, and stress. Among clinical and community populations high internal consistency was found for the depression (α=0.94), anxiety (α=0.87), and stress subscales (α=0.91). The DASS-21 has also been found to have good convergent reliability with other well validated measures of depression and anxiety (e.g., Beck Depression Inventory, State-Trait Anxiety Inventory). Parents and adolescents will complete this about themselves.

Eating Disorder Flexibility Index (EDFLIX): The EDFLIX is a 51-item questionnaire where participants use a six-point Likert scale to respond to each question. The EDFLIX ranges in

questions, some asking specifically about their eating disorder (e.g., "I need my meals to be predictable (time, food, content)" and "I prefer eating the same foods as I usually do") and others are more abstract (e.g., "I find it difficult to get used to new situations" and "When I am stuck on a task, I am unable to come up with new solutions.")

Autism Spectrum Quotient (AQ-10): The AQ is a 10-item questionnaire for parents to complete regarding the child's behavior if their child is between 12 and 15 years old. If the child is 16-18 years old, the child will complete this questionnaire about themself. Additionally, parents will complete this questionnaire about their own behavior. The AQ contains a 4-point scale, ranging from "definitely agree" to "definitely disagree." There are two versions of this questionnaire, one for participants aged 12-15 years old and another for participants aged 16 and older. Examples of questions are, "S/he notices patterns in things all the time" and "S/he is good at social chit-chat."

Social Reward Questionnaire (SRQ): There are two versions of the SRQ, one for adults and one for adolescents. We will administer the SRQ designed for adolescents (SRQ-A). This 20-item questionnaire is scored on a 7-point scale, with responses ranging from "Strongly disagree" to "strongly agree." The questionnaire asks participants to rate different statements such as, "I enjoy treating others fairly" and "I enjoy keeping promises I make to others."

Parent Versus Anorexia Scale (PVA): The PVA is a 7-item questionnaire for parents to complete regarding their own self efficacy to feed their adolescent. They respond to each item on a 5 point Likert scale ranging from "strongly disagree" to "strongly agree". It is aimed at measuring parental efficacy throughout family-based treatment to track changes over time.

Treatment Credibility/Alliance

Credibility/Expectancy Questionnaire (CEQ;[84]). This 6-item questionnaire measures both cognitive and affective elements regarding how much individuals believe in, and expect they will improve, due to treatment. The CEQ was designed to be used in clinical outcome trials and was validated on a mixed sample of patients. It has good internal consistency (.85) and test-retest reliability (.75-.82).

Working Alliance Inventory (WAI;[85]). The WAI is a 36 item measure that assesses goals, tasks, and the bond present in therapy. It can be completed by the therapist, client, or an observer. Reliability ranges from .89-.93. Therapeutic alliance is recognized as an important contributor to outcome, however, adolescents with AN have been reported to demonstrate deficits in forming a strong therapeutic relationship and this may impact outcome.

CRT Treatment Evaluation Questionnaire (TEQ;[86]) The TEQ is a 20-item measure that assesses how participant feel about CRT, including the perception of change, view of the therapist, treatment satisfaction. It is completed at the end of treatment and will only be completed by the individuals who receive CRT. It currently does not have published reliability statistics as it is a relatively new measure.

5.2 Efficacy Evaluations

There is no efficacy evaluation. The purpose of this study is to determine whether or not CRT can improve flexibility in the parents or the adolescent. We will gather data on efficacy in future work.

5.3 Safety Evaluation

Subject safety will be monitored by adverse events, weight, parental report of behavior, and weekly checks on eating disorder symptoms (EDE short version). Regular contact with the adolescents' pediatricians will also occur. When questions may arise about adolescent health, Dr. Peebles will review vital signs, weight gain, and eating disorder symptoms and make recommendations vis a vis hospitalization or referral to a higher level of care.

6 STATISTICAL CONSIDERATIONS

6.1 Primary Endpoint

Aim 1: To identify whether or not it more impactful to add a parent or adolescent component of CRT to standard FBT. To assess if CRT engages the target, we will use mixed 3 (treatment) x 2 (time) Multivariate Analysis of Covariance (MANCOVA): one for adolescents, one for mothers, and one for fathers. The covariate for all analyses is total IQ on the WASI. Dependent variables are as follows: Trails Number-Letter Sequencing, Inhibtion, Inhibition/Switching, Correct Response Shifting, Category Switching, or Description 1 or 2 and Shift on the BRIEF-2. We will follow these steps:

1. Conduct omnibus MANCOVA and evaluate significance. If not significant, stop and move to next analysis.

2. If the omnibus test is significant, we will conduct individual 2 (treatment) X 2 (time) Analysis of Covariance (ANCOVA) to determine which dependent variable had significant change, with IQ again as the covariate.

3. Each assessment of the target (DV) will be examined. Results will inform the Go/No-Go Decision as described in Table 6.

These three steps will be repeated for adolescents, mothers, and fathers. We will include all three groups in the initial MANCOVA and follow-up with planned comparisons (ANCOVA) of FBT vs the appropriate CRT condition. In all analyses, we will focus on the within and between-group effects, examining interaction effects are not necessary to evaluate the target. As we have chosen measures demonstrated to change with CRT,[40,87-90] we will maintain α=0.15 for each analysis.[91] We do not expect adolescents whose parents receive CRT or parents whose adolescents receive CRT to demonstrate increases in flexibility. However, should the planned ANCOVAs not be significant, we will be able to explore other possible group differences. Additionally, we will explore the relationship between dependent variables via discriminant analysis. These additional methods to examine the data will not factor into the Go/No-Go decision, but will enhance the depth of our understanding of the data and contribute to our understanding of neurocognition in AN.

Aim 2: To determine the dose of CRT needed to lead to a medium effect size. Some research indicates that ≥8 sessions of CRT are necessary for improvement in cognitive flexibility with AN.[92] It is unknown how many sessions will be needed for significant change in parents of

adolescents with AN. To determine optimal dose, we will model change across the 15 sessions using latent growth curve modeling (LGCM). LGCM will allow us to analyze individual and average trajectory and model linear and quadratic trend. We will visually assess for the point (dose) at which there is a significant decrease in the *rate* of improvement (quadratic). Parameter estimation will employ Maximum Likelihood (ML) estimation.[93,94] We will evaluate model fit using chi-square (χ^2), Comparative Fit Index (CFI), Standardized Root Mean Squared Residual (SRMR), and Root Mean Squared Error of Approximation (RMSEA).[95] The following values are indicative of acceptable fit between the model and the observed data variance/covariance matrixes: CFI, SRMR, and RMSEA, < .95, < .80, and < .05, respectively. We will assess and compare different models using BIC and novel criteria such as Scaled Unit Information Prior BIC.[96,97] Examining standardized model residuals in addition to global fit indices (GFI) permits us to identify model misspecification even if GFI values suggest adequate fit.[95]

6.2 Secondary Endpoints

Secondary endpoints include preliminary examination of symptom change (EDE, ABOS) and rate of weight gain.

6.3 Statistical Methods

6.3.1 Baseline Data

Baseline and demographic characteristics will be summarized by standard descriptive summaries (e.g. means and standard deviations for continuous variables such as age and percentages for categorical variables such as gender).

6.3.2 Safety Analysis

All participants enrolled will be included in the safety analysis. Frequency of hospitalization and referral to a higher level of care will be summarized. Differences between those who need hospitalization and those who do not over the course of the study will be explored and reported.

6.4 Sample Size and Power

Power analysis Aim 1. In the initial phase of the proposed project (R61), our sample size estimation is based on a mixed MANCOVA design with two repeated measures from baseline to end-of-treatment (EOT; within subjects component) and three groups (CRT_P, CRT_A, and FBT; between subjects component). Based on a review of the literature, we are powering for a medium effect size. Our effect size estimate is Cohen's f statistic.[98] This effect size estimate is a ratio of variation explained to that unexplained by the model (treatment groups), and is expressed as follows: $f = \sqrt{\frac{\eta^2}{(1-\eta^2)}}$, where $\eta^2 = \frac{\sigma^2_{model}}{\sigma^2_{Total}}$; proportion of variability due to the model.[99,100] Heuristics for small, medium, and large effect sizes are .1, .25, and .4, respectively. We selected an alpha of 0.15, given the nature of the study and the difficulty in recruiting participants from a low prevalence condition. Alpha of 0.15 is essential to provide adequate power for this study.[91] As any analysis powered for a medium effect will also be powered for a large effect, we only highlight the expected medium effect. For all analyses, we specified an α=0.15, two time points, and a correlation between measures of .3 (based on unpublished data). The anticipated N accounts for dropouts (i.e., number enrolled will be higher).

Power analysis Aim 2. Using Mplus 7.2,[94] we conducted a LGCM Monte Carlo simulation with 1000 replications[94,101-103] to determine power to identify $CRT_{P/A}$ dosage based on a half standard

deviation increase (rate of change; slope) from baseline (effect size) above FBT. With 15 participants in 3 groups across 5 time points, parameter and standard error bias were ≤ 5%, confidence interval coverage ≥ 90%, and power = 0.59.

7 STUDY MEDICATION (STUDY DEVICE OR OTHER STUDY INTERVENTION)

7.1 Description

All treatment will be delivered by a doctoral- or Master's-level psychologist. All therapists will be trained in FBT and CRT and will have their adherence to the manual supervised by the PI. These clinicians will be designated and added to section 1.02 of the eIRB once hired. Treatment will be delivered at the Robert's Center for Pediatric Research.

7.2 FBT

FBT was described in section 1.2.1. 15 sessions of FBT will be administered over the course of 6-12 months, with the option to participate in an additional 12 follow-up FBT sessions.

7.3 CRT

CRT was described in section 1.2.2. 15 sessions of CRT will be administered over the course of 6 months for families in CRT_A and CRT_P.

7.3.1 Treatment Compliance and Adherence

Treatment Fidelity. Sessions will be conducted by doctoral- or Master's-level therapists with training in FBT for AN. Prior to study start, therapists will attend a 3-day workshop with the PI. The first day reviews FBT; days 2-3 provide training in CRT. Dr. Timko will provide weekly supervision of FBT and CRT.

Treatment sessions will be videotaped and a random selection of 20% tapes per patient will be reviewed for adherence to FBT and CRT. FBT fidelity will be assessed using published methods,[104] CRT fidelity will be assessed by measures developed by the PI and used in a recent CRT pilot study. A trained master's level research assistant will score tapes for adherence and review weekly with Dr. Timko. In the event that a participant receives care that is a significant deviation from protocol (lack of adequate adherence ratings on more than 20% of sessions), this participant's data will be removed from analyses. If drift occurs, therapists will complete a refresher training session, the next three sessions will be reviewed and if improvement to criterion does not occur, the therapist will be withdrawn.

Missed sessions. Should a therapist miss a session (due to illness or vacation) the session will be rescheduled, the other therapist will see the family to ensure that a week is not missed, or the family will be asked to schedule two sessions the following week. Should the family need to cancel, all attempts will be made to reschedule within the week to ensure the family stays on schedule. If an appointment cannot be rescheduled within the week, the family will have two sessions scheduled the following week.

8 SAFETY MANAGEMENT

8.1 Clinical Adverse Events

Clinical adverse events (AEs) will be monitored throughout the study.

8.2 Adverse Event Reporting

Since the study procedures are not greater than minimal risk, SAEs are not expected. If any unanticipated problems related to the research involving risks to subjects or others happen during the course of this study (including SAEs) they will be reported to the IRB in accordance with CHOP IRB SOP 408: Unanticipated Problems Involving Risks to Subjects. AEs that are not serious but that are notable and could involve risks to subjects will be summarized in narrative or other format and submitted to the IRB at the time of continuing review.

8.3 Medical Emergencies

As hospitalization for medical stabilization can occur during routine treatment, hospitalization will not be considered an SAE. A summary of all hospitalizations for medical stabilization will be provided at the time of continuing review.

9 STUDY ADMINISTRATION

9.1 Treatment Assignment Methods

9.1.1 Randomization

Procedures for randomization were described in Section 3.2.

9.1.2 Blinding

Research assistants who assess adolescents at each time point will not be aware of their study condition.

9.2 Data Collection and Management

All data (with the exception of DKEFS, WASI, BRIEF, and BASC as these have standardized forms) will be stored in RedCap. Scores from these standardized forms will be entered into RedCap to ensure all data is in the same place.

All participants will be given a unique study ID and all study information will be coded using this number (in RedCap and on standardized forms). The master list linking participants with their numbers will be stored in a separate RedCap file that only members of the research team will have access to.

RedCap data will be downloaded weekly and stored in a password protected file on the secure research server. Only the CRC and PI will have the password. This is for backup.

Audio/video files of treatment sessions will be stored on the research server and destroyed after study end. These are necessary to ensure treatment fidelity. Only study staff involved in the project will have access to these files.

Data will remain coded until all study procedures are complete and initial findings have been published. After 6 years, the list linking study IDs to participants will be destroyed. Remaining data will be retained indefinitely.

9.2.1 Data sharing

Per NIH requirements, data will be shared via the National Database for Clinical Trials related to Mental Illness. Within 3-months of the award, the PI will complete a NIMH Data Repositories Data Submission Agreement. Per guidelines, data will be shared in two tiers: raw data while the study is on-going and analyzed data with publication of results/after the reward period. Once a manuscript is published, all analyzed data will be submitted. Data will include descriptive/raw day from questionnaires, demographic data, and data abstracted from the medical chart. We will also include raw and standard scores for the neuropsychological assessments used in the course of this study. Per requirements, raw data will be submitted bi-annually, starting 6 months after project begin. Given the novel aspect of behavioral data (Howe's Grocery and Buffet Challenge), we will work with staff in order to ensure appropriate and smooth submission of data. Video recordings of the buffet challenge will not be submitted. Additionally, video recording of the clinical interviews will not be submitted. We will ensure that all participants will have a Global Unique Identifier and each data set will be associated with the appropriate publications.

The PI will encourage anyone who is interested in accessing the data to use the National Database. As some researchers may not have access to or wish to access the National Database,

we will make a cleaned, de-identified data set and codebook available for request 6 months after complete study end and the publication of initial manuscripts. The data will be made available to other researchers under a data sharing agreement that will provide for a commitment to using the data for research purposes and to destroying or returning the data after analysis are completed. Researchers can request the data from the PI via email. Requests are necessary given the nature of the data; although it will be de-identified, it will contain sensitive health information about the participants.

9.3 Confidentiality

All data and records generated during this study will be kept confidential in accordance with Institutional policies and HIPAA on subject privacy and that the Investigator and other site personnel will not use such data and records for any purpose other than conducting the study.

No identifiable data will be used for future study without first obtaining IRB approval. The investigator will obtain a data use agreement between the provider (the PI) of the data and any recipient researchers (including others at CHOP) before sharing a limited dataset (PHI limited to dates and zip codes).

9.4 Regulatory and Ethical Considerations

9.4.1 Data and Safety Monitoring Plan

Data and safety will be monitored on multiple levels. The PI has primary responsibility of study oversight and will meet with study staff regularly to monitor study progress, safety issues, recruitment progress, attrition, and data quality. Dr. Timko will meet as needed with the Medical Safety Officer to review new patients or any concerns.

We will monitor participants for the occurrence of any adverse events associated with data collection and participation and will report these events as directed by the institutional IRB and adverse event (AE) reporting policies. Events will be reported promptly to Dr. Timko (PI) and the study coordinator who will make provisions to respond appropriately, ensuring referral to medical/professional resources, as needed.

9.4.1.1 Breach of Confidentiality.

The PI will ensure that all members of the study team have completed all mandatory confidentiality statements and research ethics trainings and that data have been handled and stored properly. Annually, research staff will be required to sign a statement acknowledging their receipt and understanding of the confidentiality requirements and pledging to maintain confidentiality of the data to which they have access. If a breach of confidentiality is identified, the PI will immediately meet with IRB and data security leadership to review and identify how the breach occurred and to review and discuss steps to prevent future problems with ensuring participant confidentiality.

9.4.1.2 Continuous Quality Assurance and Quality Control Procedures (QA/QC)

QA/QC will be implemented to ensure compliance with study requirements in areas including recruitment and data collection. Quality control activities will be performed regularly on all electronic data and participant files to ensure that all data collected is complete and accurate. These will include the reconciliation of data forms, verification of codes and labels, and careful

review of each individual data field for omission and errors. All neuropsychological assessments will be scored twice for reliability and all data will be entered into the database twice to ensure accuracy.

In terms of day-to-day safety monitoring, the therapist will track weight, eating disorder symptom information, and closely monitor suicidality, self-harm, and other concerns. If a therapist becomes aware of suicidal or homicidal ideation or serious self-harm behavior, the adolescent will undergo a comprehensive assessment of plan and intent and the necessary precautions will be taken to insure safety or medical attention as appropriate. Standard clinic practice is for therapists to make judgments about mental status, global symptom severity, and symptom improvement at each visit and this information becomes part of patients' permanent clinical records. Participants in the study will have CHOP behavioral health emergency numbers.

9.4.1.3 Data and Safety Monitoring Board

This study will be conducted under the guidance of a Data Safety and Monitoring Board (DSMB). The DSMB will act in an advisory capacity to monitor participant safety, evaluate the progress of the study, and review procedures for maintaining the confidentiality of data and the quality of data collection, management, and analyses. The Board will be led by a chair and at least 3 additional members. Board members will have expertise in an area relevant to the study aims, examples are: adolescent health research, behavioral treatment, neuropsychology/neurocognition, treatment implementation, statistical analysis, adolescent development, and/or eating disorders. DSMB members will have no direct involvement with the study investigators or intervention. The board will meet 4 times during the study. Board members will review study progress, data quality, and participant safety. The first meeting will occur prior to initiation of study activities to review and approve the study protocol and safety monitoring and reporting plan. Subsequent meetings will occur 6 months after the start of study recruitment, 12 months after the start of study recruitment, and again after all treatment has ended and data analysis has begun. Ideally, all meetings will be in person, however, remote participation (i.e., via Skype or Zoom). A detailed DSMB Charter will be developed that provides a detailed list of DSMB responsibilities.

The DSMB will receive a data and safety monitoring report at each scheduled meeting. This report will include the following sections: Overview of DSMB, Study Status, Study Recruitment, Study Enrollment, Study Randomization, Participant Characteristics, Study Data Collection, Regulatory Compliance, Adverse Events and Protocol Deviations, Quality Control and Data Management, Data Analysis, Sample Size and Power Analysis, Outcome Data, Recent Publications of Relevance, and Challenges and Resolutions. In these reports, data and discussion will be confidential and participant identities will not be revealed.

9.4.2 Risk Assessment

Risks are not greater than minimal. The treatments being used in this study are close to routine care and do not carry a great risk of harm.

Completion of the measures can be burdensome, however, we have taken step to reduce the burden and any fatigue by breaking up questionnaire completing with neuropsychological

testing. Participants are allowed to take breaks as needed and are given time to eat snacks. A similar procedure has been used in prior research by the PI and was tolerated well by families.

The buffet challenge may be difficult for adolescents at the beginning of treatment and videotaping may be stressful for the adolescent. Parents will be made aware of the challenge and will be able to provide the adolescent with snack after the buffet is complete. As the initial clinical interview occurs at the end of intake, any concerns will be able to be addressed with the therapist.

9.4.3 Potential Benefits of Trial Participation

FBT is the gold standard of treatment. Families will receive guidance and support in refeeding their child. Most adolescents should gain weight and experience a reduction in eating disorder symptoms. CRT is highly acceptable and has been shown to decrease drop out from treatment.

9.4.3.1 Indirect benefit

More treatments for anorexia are needed, particularly for those who do not fare well in FBT. This study investigates whether or not CRT can be a viable augmentation to treatment and for whom (parents or child) it has the most benefit.

9.4.4 Risk-Benefit Assessment

Risks are minimal. All adolescents will receive family-based treatment – the most recommended treatment for adolescents with AN. Two groups will receive an additional session of CRT each week. Adolescents will be required to have medical care during the course of the study. If they are not improving, recommendations for a higher level of care will be given. The benefits of finding a way to improve outcomes out-weighs the minimal risk.

9.5 Recruitment Strategy

Eligible participants will be identified through the inpatient and outpatient programs of the Eating Disorder Assessment and Treatment Program (EDATP) at CHOP. We will also recruit through CHOP satellite primary care facilities and online.

Adolescents enter our program through three primary pathways: through an outpatient nutrition and medical evaluation, through an outpatient multidisciplinary evaluation (psychology/psychiatry, nutrition, medical), or through hospitalization for medical stabilization of complications resulting from malnutrition. Screening for eligibility will occur either at an outpatient evaluation or during hospitalization for medical stabilization.

Potentially eligible patients identified (those in hospital with a diagnosis of anorexia or those presenting for an evaluation) will be contacted in advance of their appointments and informed they may be eligible for participation in research. If the family is interested, study procedures will be described to the family, including a brief review of inclusion and exclusion criteria. If the family is interested, consent to participate will be coordinated with the clinical intake. Assuming the adolescent is stable for outpatient treatment, they can enter the research study after the intake. The study staff will only collect private health information as it pertains to determining eligibility before consent, per CHOP IRB guidelines. Study staff will not collect any additional private health information without obtaining consent and HIPAA authorization first. As the Eating Disorder Program also has an inpatient program, the list of patients being treated as part of the

adolescent service will be reviewed daily. Eligible families will be contacted during the hospital stay via direct communication with study team members or by handouts in the informational packet provided to families at the beginning of the hospital study. Families who are interested can receive information and undergo consent and parts of the assessment while in hospital, should they desire. The remainder of the assessment, randomization, and beginning of treatment in the study protocol will begin after discharge from hospital.

In order to meet recruitment goals, we will augment the above procedures by advertising the study on the CHOP website as well as external websites such as FEAST. If a participant family reaches out to the study team based on internet announcements, tearpads, or fliers, general information about the study will be provided over the phone and, if interested, the family will have a limited phone screen to determine eligibility. If the adolescent and parents are eligible to participate, study staff will schedule the family for the baseline assessment. If the family is not receiving medical care in the EDATP, medical records will be requested from the PCP. The medical safety officer (R. Peebles) will review the chart and make a recommendation regarding appropriateness for outpatient care.

Additionally, this study will appear in "This Week @ CHOP," a segment in an internal newsletter made available to all CHOP employees. Interested families will be instructed to call study staff to determine eligibility, as outlined above.

Furthermore, the study team will be obtaining a list from CHOP's Department of Biomedical Health Informatics (DBHI) of Medical Record Numbers (MRNs) of patients with an anorexia nervosa diagnosis within the last six months. Should they wish to, the DBHI could obtain this list of MRNs from the Recruitment Enhancement Core (REC), who has already pulled this data. Because we do not intend for the REC to act as an honest broker on our study team's behalf, the REC will supply the DBHI with this information, which will then be supplied to our research team. When this list is obtained, the study team will communicate with eligible families to provide more information about this clinical trial if interested. We chose not to use the REC as an honest broker as we felt that it would potentially be overwhelming for families who have opted not to participate, are already involved in care, or otherwise not appropriate for the study. We will be able to compare the list of MRNs to those who have been screened and only approach those patients who have not been screened, if appropriate. With this approach, we hope to possibly identify adolescents who are being treated in primary care without behavioral health support.

9.6 Informed Consent/Assent and HIPAA Authorization

Informed consent will be obtained by research assistants. Consent will take place prior to the intake and will occur at Robert's Center for Pediatric Research prior to the intake. For adolescents who are hospitalized for medical stabilization and preparing for discharge to outpatient treatment, consent can occur while they are in hospital at CHOP.

Participants will be able to take up to 48 hours to make a decision about participation in the study. Should they ask to reschedule the intake after study procedures have been reviewed, this request will be accommodated. Any and all questions will be answered by the study team member reviewing the consent form. All risks and benefits will be explained. In prior research the consent procedure usually takes 30 minutes.

The consent form will be signed by parents, the adolescents, and a member of the study team. HIPAA Authorization will be combined with the consent form. Parents will be given a copy of the consent form to take home with them.

Consent and assent will be obtained from subjects who are 14+ years old and from parents. For all other adolescents, we will waive assent. This is in line with the Patient Care Manual Policy: Storage and Release of Mental Healthy Record stating that subjects who are 14 years old must provide their own consent for mental health treatment and for the review of their mental health records and must provide their own assent for participating in the research study.

Consent will ideally occur in-person; however, if this is not possible then remote consent will occur. Remote consent will take place on a CHOP-approved video conferencing platform, and study staff will review all sections of the informed consent form with families. Families will be sent a link to our REDCap project with the informed consent form. At the end of the informed consent discussion, families will be asked to e-sign and e-date in the appropriate sections of the REDCap project. An electronic copy of the informed consent form will also be sent to the families for their records.

9.6.1 Waiver of Assent

We are requesting a waiver of assent for all subjects <14 years old. Adolescents with AN are in a state of acute malnutrition and starvation. This can impact their executive functioning and ability to understand what is being asked of them. In addition, anosognosia is common in AN and many adolescents do not recognize the fact that they are ill or understand the severity of their illnesses. Given the high morbidity and mortality rate in AN, requiring adolescent assent could delay treatment.

9.7 Payment to Subjects/Families

9.7.1 Reimbursement for travel, parking and meals

Families will be given a parking pass for each visit to Robert's Center for Pediatric Research so that they do not have to pay for parking.

9.7.2 Payments to parent for time and inconvenience (i.e. compensation)

Time point 1: $50/parent for completing questionnaires, neuropsychological assessment, and Grocery challenge

Time point 2: $10/parent for completing the questionnaires

Time point 3: $25/parent for completing the questionnaires and neuropsychological assessment

Time point 4: $35/parent for completing questionnaires, neuropsychological assessment, and Grocery challenge

Time point 5: $50/parent for completing questionnaires, neuropsychological assessment, and Grocery challenge

Time point 6: $5/parent and $5 for adolescent for completing questionnaires

Time point 7: $5/parent and $5 for adolescent for completing questionnaires

9.7.3 Payments to subject for time, effort and inconvenience (i.e. compensation)

Time point 1: $50/subject for completing questionnaires, neuropsychological assessment, and Grocery challenge

Time point 2: $10/subject for completing the questionnaires

Time point 3: $30/subject for completing the questionnaires and neuropsychological assessment

Time point 4: $35/subject for completing questionnaires, neuropsychological assessment, and Buffet challenge

Time point 5: $50/subject for completing questionnaires, neuropsychological assessment, and Buffet challenge

9.7.3 Gifts

The study team will send thank you cards after each assessment and give the family a refrigerator magnet as a reminder of participation.

10 PUBLICATION

This is the first phase of a two-phase study (R61/R33 mechanism). We must show improvement in the target and meet a-priori Go/No-Go criteria in order to move forward after year 2. Data gathered will initially be used to answer the Go/No-Go question. The publication time line would impacted by this funding decision. Data will be presented at conferences and published as appropriate.

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