Reward Re-Training: A New Treatment to Address Reward Imbalance During the COVID-19 Pandemic

Study Protocol

NCT04661410

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RESEARCH STRATEGY

A. Background and significance

A.1. Public health approaches to combat COVID-19 have caused large disruptions in social networks.

Public health approaches to reducing the spread of COVID-19 such as social distancing, shelter-in-place orders, quarantine, telework, and remote learning have produced a sudden and widespread disruption to social networks. These large disruptions to social networks are likely to increase social isolation (i.e. limited interactions, contacts, and relationships with family, friends, romantic partners, or co-workers) and loneliness (i.e. an adverse emotional state characterized by a lack of connection and intimacy),[1] particularly for those living alone[2] or those who already felt isolated before the outbreak.[3] This is particularly concerning given the strong evidence that social isolation and loneliness are transdiagnostic risk factors for a range of mental health disorders[4], strongly associated with increased risk of suicidality[5], and have a comparable or greater impact on mortality than other common risk factors such as obesity, physical inactivity, and smoking.[6]

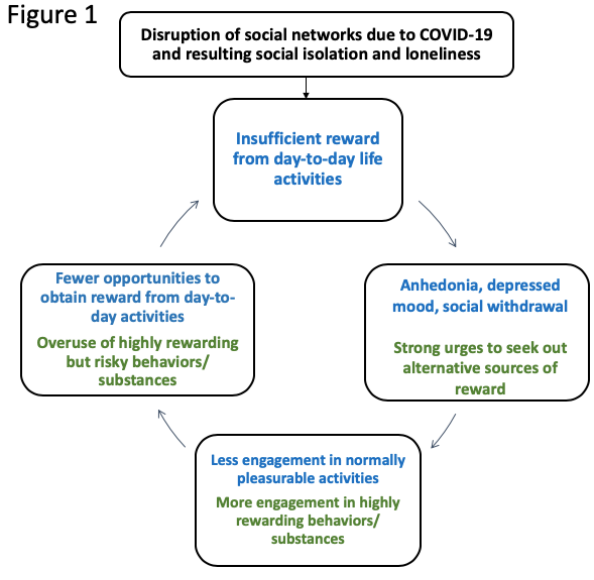
A.2. Social isolation can exacerbate mental health concerns by limiting opportunities to experience pleasure and reward during day-to-day life.

We have long understood that social interactions are among the most powerful sources of pleasure and reward in day-to-day life.[7-10] Yet, as noted above, during the COVID-19 pandemic, individuals are increasingly being encouraged or required to intentionally limit opportunities for social reward by staying at home and minimizing in-person contact with family, friends, classmates, and colleagues.[11] Reduced exposure to sources of reward can lead to a hypo-reward response (e.g. low activation of dopaminergic cortico-striatal reward pathways) to conventionally rewarding stimuli[11] (particularly to social stimuli and interactions[12]) and reduce an individual's motivation to engage in activities that they usually find pleasurable.[13] Motivation to engage in typically pleasurable activities will often continue to worsen over time as any engagement in activities that does occur is insufficiently reinforced due to the low levels of anticipatory and consummatory reward experienced.[13] Thus, over time, a vicious cycle can occur such that day-to-day opportunities to experience reward become increasingly limited and anhedonia and depressed mood may begin or worsen.[14] This cycle (depicted in blue text in Figure 1 below) has long been recognized as a maintenance factors for depression[15-17] and disrupting this cycle is a key goal of effective treatment approaches for depression such as behavioral activation.[18, 19]

A.3. Low levels of day-to-day reward may also be a relevant maintenance factor for mental health conditions characterized by compulsive engagement in or use of highly rewarding stimuli.

There is a growing body of evidence to suggest that insufficient reward from day-to-day life activities is a relevant maintenance factor for many mental health conditions beyond depression.[20-24] In particular, mental health conditions characterized by compulsive engagement in or use of highly rewarding stimuli despite adverse consequences (e.g. substance use disorder, behavioral addictions, eating disorders) appear to be maintained, in part, by insufficient reward from day-to-day life activities. When day-to-day life activities are not providing enough reward, these individuals may be more likely to seek out other stimuli that can immediately and powerfully activate neural reward pathways such as illicit substances or to over-indulge in naturally rewarding behaviors such as the consumption of palatable foods.[25-27] A hyper-reward response (e.g. high activation of dopaminergic cortico-striatal reward pathways) to disorder specific stimuli (e.g. the feel of holding poker chips, the smell of highly palatable food, sexual imagery) may develop as individuals seek out larger quantities or more frequent exposure to a limited range of intensely stimulating sources of reward. We propose that these individuals may become stuck in a second vicious cycle (depicted in green text in Figure 1) whereby increasing reliance on one behavior/substance to provide reward further reduces the ability to experience reward from day-to-day life activities, which then subsequently drives continued engagement in highly rewarding but risky behaviors. Together, the blue and green pathways in Figure 1 comprise what we have termed a reward imbalance. While the reward imbalance is likely an important maintenance factor outside of the COVID-19 pandemic, the resulting disruptions to social networks are almost certainly exacerbating this cycle as depicted in Figure 1.

Figure 1



A.4. The impact of COVID-19 on the reward imbalance underlying binge eating may be particularly pronounced and require targeted interventions.

There is a strong and growing body of evidence supporting reward imbalance as an important maintenance factor for individuals with an eating disorders (ED) characterized predominately by binge eating episodes (i.e. eating a large amount of food within a discrete time period accompanied by a sense of loss of control over eating). Individuals with bulimia nervosa (BN) and binge eating disorder (BED) show clear evidence of both insufficient reward from day-to-day-life activities (e.g. elevated rates of anhedonia[21, 22, 28, 29]) and a hyper-reward response to palatable foods.[30-33] Recent studies suggest that momentary assessment of constructs indicative of insufficient reward such as low levels of positive affect[34-36] and bordeom[37, 38] can predict increased risk for the near-time occurrence of a binge eating episode. Collectively, these results provide preliminary support for reward imbalance as a maintenance factor for binge eating.

Individuals with EDs may also be particularly vulnerable to the disruption of social networks during COVID-19 given the clear evidence that even before the pandemic, individuals with EDs were more likely to be socially isolated,[39-41] spend more time alone,[42] have greater rates of social anxiety,[43] experience worse social functioning,[44], and have worse quantity and quality of social support [45] compared to peers without an ED. Accordingly, there is emerging evidence suggesting an outsized impact of COVID-19 on ED symptoms[46, 47] likely due to the combined impact of heightened stressors, disrupted routines, and diminished social support paired with constant and easy access to food within the home that can trigger binge eating episodes. For example, in a recent study examining the impact of the first two weeks of stay-at-home orders on EDs, over 50% of the sample reported heightened anxiety and nearly 40% reported a worsening of ED symptoms.[48] Accordingly, many individuals with EDs are urgently seeking additional treatment resources to cope with the new challenges they are experiencing. In March and April, the National Eating Disorders Association reported a 78 percent increase in people messaging its help line compared with the same period last year.[49] Similarly, the Crisis Text Line, a nonprofit organization that provides mental health support by text, reported a 75 percent increase in conversations about eating disorders in the two months since March 16.[49] These results align with our own experience of increased treatment seeking among individuals with EDs in recent months. For example, in response to an advertisement placed on Facebook in June 2020 about a fully remote group-based clinical trial for individuals with binge eating disorder (R01DK117072), we had 480 individuals complete our online interest survey in a 4-day time period, with over 130 individuals meeting preliminary eligibility criteria. The high level of interest in treatment has resulted in a large waitlist of likely eligible participants (see *Recruitment and Retention Plan* for more details). These results suggest a clear and pressing need to develop and deliver highly scalable treatment approaches for binge eating during the COVID-19 pandemic.

A.5. Reward Re-Training: A novel intervention approach designed to alter the reward imbalance.

Prior to the COVID-19 pandemic, our team began to develop and pilot a novel treatment approach called Reward Re-Training (RRT) that is specifically designed to address reward imbalance. Although we believe that RRT could be an effective treatment approach for numerous mental health conditions, we developed our initial version of RRT for individuals with transdiagnostic binge eating. RRT is designed to be a brief, 10-session group-based behavioral treatment. One unique aspect of RRT compared to traditional behavioral treatment approaches for EDs is that RRT does not directly attempt to reduce binge eating episodes via commonly used behavioral treatment components such as regular eating interventions and self-monitoring of food intake.[50] Instead, RRT is designed to <u>indirectly</u> change binge eating by <u>directly</u> focusing on building a more rewarding life. RRT hypothesizes that reductions in binge eating will occur as life becomes more rewarding because individuals will no longer need to rely on binge eating as a primary source of momentary reward. RRT notes that in order to live a satisfying life, individuals need to experience an adequate amount of reward in two overlapping yet distinguishable domains: momentary reward (i.e., the active experience of pleasure in the moment) and sustained reward (i.e., a deeper and more long-lasting sense of fulfillment and meaning that arises from building a personally valued life). A key aspect of RRT is an emphasize on building lasting and meaningful social relationships given the clear evidence that social connectedness can enhance both momentary reward and sustained reward.[7]

<u>A.5.1. Increasing momentary reward outside of binge eating.</u> RRT frames the use of binge eating as a source of momentary reward as risky since binge eating will 1) likely provide less momentary reward over time due to tolerance and habituation, 2) increase short-term negative affect (e.g. guilt, regret, and shame), and 3) undermine attempts to increase sustained reward by continuing the cycle depicted in Figure 1 above. Based on evidence that pleasant event scheduling (an evidence-based component of behavioral treatments for

depression that seeks to increase momentary reward by increasing pleasant experiences, social activity, and completion of productive tasks[18, 19]) can improve anhedonia over time, we chose to use pleasant event scheduling as the starting point of RRT. Individuals are instructed to continue engaging in pleasant event scheduling even if the new activities do not immediately provide significant momentary reward by emphasizing the need to "re-train" reward networks away from eating and towards these new activities through repetition and practice. RRT also encourages the use of several additional cognitive and affective strategies designed to facilitate and enhance the ability to experience reward from conventionally rewarding activities. For example, RRT teaches patients how to shift attention towards positive momentary experiences and how to reframe affective experiences to allow room for multiple emotions.

A.5.2. Enhancing sustained reward by building a personally valued life. RRT emphasizes that in order to truly correct the reward imbalance, we must identify what a satisfying and fulfilling life would look like and start to build a life that will feel personally valued. RRT uses techniques from evidence-based treatments like acceptance and commitment therapy[51] to help an individual clarify his or her values (defined as global, desired and chosen life directions[52]) to inform the selection of behavioral patterns that will be built during treatment. For example, if an individual determines that he values supportive friendships but reports having few friendships currently, a major emphasis of treatment would be on identifying how to change his lifestyle to expand his social network and enhance the quality of his existing friendships. This work may include identifying new activities where he may be likely to meet individuals with shared interests, facilitating more frequent contacts with his current social connections, and learning social communication strategies to build greater intimacy within his friendships. RRT acknowledges that the process of building a life that will provide sustained reward will at times be difficult, uncomfortable, and distressing. In the above example, developing close and supportive friendships may be stressful or anxiety provoking and could introduce the possibility of rejection, none of which will feel pleasurable in the moment. RRT provides new techniques designed to make the process of pursing sustained reward also provide momentary reward. For example, RRT teaches individuals how to experience a sense of self-efficacy and personal achievement whenever he or she makes a difficult behavioral choice that supports the development of a valued life capable of providing sustained reward. In this way, RRT supports individuals in their pursuit of a valued life by ensuring that there is also sufficient momentary reward (e.g. achievement, confidence, pride) that can reinforce these new values-consistent behaviors.

A.5.3. Increasing the quantity and quality of social interactions. When choosing pleasant events, RRT specifically encourages individuals to prioritize activities that are social in nature given evidence that these activities tend to be more enjoyable in the moment than solitary activities.[10, 53] Similarly, given that for most individuals, meaningful and fulfilling relationships are among the most important valued life domains,[8, 10] RRT particularly focuses on building valued life domains related to relationships (e.g. romantic relationships, family relationships, friendships). RRT also teaches skills focused on how to develop and maintain high quality relationships. These include strategies for making relationships deeper and more fulfilling, strategies for building intimacy in new relationships, and effective communication strategies. Because many individuals with EDs are socially isolated and the development of meaningful relationships will take time, RRT is delivered in a group format and encourages the use of the group as an immediate source of social connection. Group members are encouraged to develop relationships with each other outside of the group setting that may last well beyond the program's short duration.

A.6. Preliminary results of RRT suggest the promise of this intervention paradigm, but additional research is needed to determine whether a fully powered trial is worth pursuing.

In a recent pilot study of RRT, we randomized 19 individuals with transdiagnostic binge eating to receive either RRT or a wait-list control. As described in greater detail in the *Preliminary Studies* section below, we found preliminary support for the feasibility, acceptability, target engagement, and clinical impact of RRT. However, despite the promise of our early pilot data, we believe that a more rigorous pilot RCT with an active control condition and with follow-up data would allow us to determine whether RRT is worth testing as a treatment approach for transdiagnostic binge eating in a fully powered clinical trial. We also believe that there is considerable benefit to leveraging our existing clinical research infrastructure (see *Recruitment and Retention* plan for additional details) to evaluate RRT during the COVID-19 pandemic given that RRT is particularly well-suited to address the disruption to social networks and resulting impact on day-to-day reward that has occurred due to COVID-19. The proposed study is consistent with the research priorities outlined in NOT-MH-20-047 (e.g. *Research to identify potential intervention targets for modifying social connectedness, isolation, and/or loneliness via social media and/or electronic communication to prevent the development of clinically significant mental health symptoms.*)

A.7. Current study and specific aims.

In the current study, we will revise our existing 10-session group RRT treatment manual to specifically address the challenges in building social support and enhancing both momentary and sustained reward during the COVID-19 pandemic (Preliminary Aim 1). In months 2-18, we will conduct a small pilot RCT that will randomize individuals to receive either 10-sessions of RRT (n=30) or supportive therapy (n=30), both delivered as group-treatments via videoconferencing software. The specific aims of the current study are to confirm the feasibility and acceptability of RRT for EDs (Primary Aim 1), evaluate the ability of RRT to engage critical targets including reward to day-to-day life activities, reward to palatable foods, social isolation, and loneliness (Primary Aim 2), and provide preliminary estimates of efficacy in reducing ED symptoms at both post-treatment and a 3-month follow-up (Primary Aim 3). We will also evaluate the impact of RRT on secondary outcome variables including depression, substance use, and quality of life (Secondary Aim 1).

B. Innovation

B.1. Treatment target innovation. To the best of our knowledge, there are no other treatment approaches for EDs that have been empirically tested that specifically attempt to improve binge eating by increasing day-to-day reward. To date, the closet evidence-based treatment approach is Interpersonal Therapy (IPT),[54] an intervention approach initially developed for depression that focuses on addressing interpersonal difficulties and works via an indirect pathway to improve ED symptoms. Meta-analyses of IPT for EDs generally suggest that while IPT tends to work less rapidly than more directive behavioral treatment approaches like CBT, it eventually reaches similar levels of efficacy and may protect better against relapse.[55] The success of IPT suggests that that it is possible to improve ED symptoms indirectly and that interventions focused on relationships can be effective in doing so. While IPT and RRT both address relationships, IPT is more narrowly focused on a specific set of relationship concerns (e.g. role disputes, role transitions, interpersonal deficits, and/or unresolved grief)[54], which may reduce the degree to which IPT could improve day-to-day reward via improvements in social relationships. RRT instead uses behavioral techniques to broadly focus on increasing momentary and sustained reward (often, but not entirely, by developing and improving social relationships) which may allow RRT to have even broader impact on ED symptoms.

B.2. Clinical innovation. As described above, RRT uses techniques from evidence-based treatments known to improve the ability to experience reward (e.g. pleasant event scheduling, values-based behavioral activation). RRT also shares features with other in-development treatment approaches that focus on increasing positive affect (e.g., positive affect treatment,[56] mindfulness-oriented recovery enhancement[57]). However, RRT is distinct in four key ways: 1) RRT focuses on increasing both momentary and sustained reward, while the majority of other treatments primarily focus on increasing momentary reward; 2) RRT is designed for use in disorders characterized by compulsive engagement in or use of highly rewarding stimuli rather than mood disorders, which is where most of the work has been done to date for behavioral activation and positive affect focused treatments; 3) RRT contains new cognitive and affective strategies designed to support individuals in their pursuit of a valued life capable of providing sustained reward by helping the process of pursing sustained reward also provide momentary reward; 4) RRT specifically focuses on increasing the quantity and quality of social activities and relationships given evidence that support the high reward value of these domains.

B.3. Dissemination and implementation innovations. While there is growing evidence that the provision of therapy via videoconferencing is an effective intervention modality,[58] the majority of existing trials have tested individual psychotherapy which can be difficult to scale during times where there is a significant increase in treatment need. The current study will be among the first to test the feasibility and acceptability of a short-term (e.g. 10 session) group-based videoconferencing treatment for EDs, which has high potential to be a disseminable and scalable treatment approach.

C. Preliminary Studies

C.1. Promising results from our prior studies demonstrate that 1) our hypotheses are likely to be supported, and 2) our team has the expertise necessary to conduct the proposed study.

C.1.1 Feasibility and acceptability of delivering remote treatments for EDs. Our team transitioned three NIH-funded clinical trials for BN and/or BED from in-person treatment to remote treatment in March 2020 due to the COVID-19 pandemic and since then have started two additional NIH-funded clinical trials that are fully remote. As outlined in greater details in the *Recruitment and Retention Plan*, we have been able to successfully transition to remote recruitment and enrollment and have seen increases in the number of individuals who are interested in participating in one of our clinical trials. In addition to high interest in remote therapy, we have also

observed increases in our attendance and retention rates and similar efficacy with the switch over to remote treatment. For example, in our ongoing group-treatment study for individuals with BED (R01DK117072) we had a new wave of groups scheduled to start one week after the stay-at-home order was implemented for Philadelphia necessitating that all group session for this wave occur via teleconferencing. Surprisingly attendance rates for the first 10 sessions of this wave of groups have been higher than for in-person groups (96.5% vs. 85.0%), drop out was lower (5.0% vs.14.0%), and reductions in binge eating by the mid-treatment assessment were slightly better (87.3% reduction in binge eating episodes compared to 71.9% reduction). Overall, these results support the feasibility and acceptability of remote treatments for EDs and demonstrate that our team has developed the infrastructure to allow for a rapid start-up to the proposed project.

C.1.2. Social isolation in individuals with BED during the COVID-19 pandemic. We administered a brief survey to individuals currently participating in R01DK117072 to assess the impact of public health initiatives to control the spread of COVID-19 on social networks (n = 21). The majority of our participants reported a significant reduction in both the frequency of social interactions (57.1%) and in satisfaction with their current relationships (61.9%) confirming that there have been widespread disruptions to social networks due to the COVID-19 pandemic in our patients.

C.1.3 RRT pilot trial. We recently conducted a small, proof-of-concept pilot trial where we randomized individuals with transdiagnostic binge eating (n=19) to receive either 10 weeks of group-based RRT or a wait-list control (WLC). RRT produced a significant reduction in binge eating episodes (Figure 2) and 40% of individuals in RRT were in remission by the end of treatment compared to 0% in WLC. Preliminary results support our targets with individuals who received RRT experiencing greater pleasure from social activities (Figure 3), more momentary reward during day-to-day life activities (Figure 4), and less reward to palatable foods (Figure 5).

Figure 2

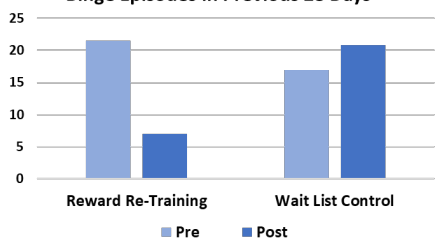


Figure 3

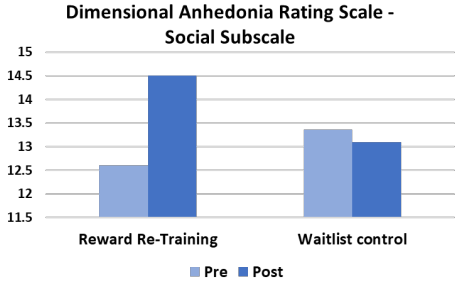


Figure 4

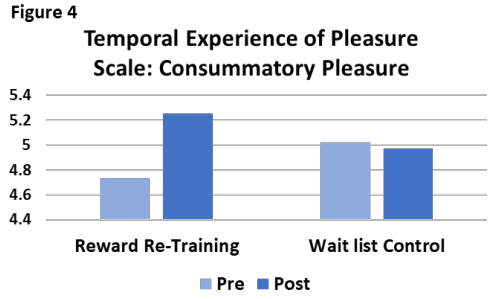
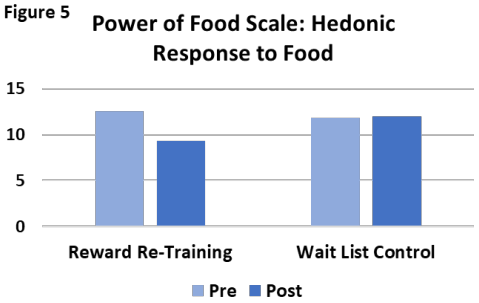


Figure 5



D. Approach

D.1. Participants. 60 participants will be recruited for this study. Participants must: A.) be age 18-65, and B.) have a diagnosis of either BN or BED. Individuals will be excluded if they are 1) below a BMI of 17.5, 2) are already receiving treatment for an ED, 3) require immediate treatment for medical complications as a result of eating disorder symptoms, or 4) are experiencing other severe psychopathology that would limit the participants' ability to comply with the demands of the current study (e.g. severe depression with suicidal intent, active psychotic disorder). Participants will be screened by phone to assess preliminary eligibility. Phone screens will use questions from the Mini International Neuropsychiatric Interview (MINI)[59] to assess psychiatric comorbidity and will be conducted by trained doctoral students, similar to procedures used successfully in our teams other NIH trials.

D.2. Refining RRT for use during the COVID-19 pandemic. In month 1, we will revise our existing RRT manual to facilitate delivery via videoconferencing software by applying "lessons learned" from our ongoing remote groups for R01DK117072. For example, we will add instructions to use video conferencing features such as breakout rooms to facilitate in-session experiential activities and whiteboards to facilitate 'real-time' collaborative problem-solving. We will also revise the content of the RRT manuals to provide guidance on ways to build and maintain social connections during the COVID-19 pandemic as in-person social contact is limited (e.g., connecting with neighbors on Facebook group, scheduling virtual game nights with friends, enhancing intimacy with romantic partners during at home dates, attending virtual happy hours with colleagues), and address disruptions in current relationships due to the pandemic (e.g., conflict due to the switch to telework/ teleschool). Participants will be encouraged (though not required) to connect with each other outside of group using email, texting, and social networking platforms to enhance social support outside of weekly sessions.

D.3. Supportive therapy as an active control condition. We considered several possible comparison conditions for the proposed trial including treatment-as-usual, the provision of self-help reading materials, and the use of a gold-standard comparison such as CBT before determining that a group-based supportive therapy condition was the best control condition for the current state of the research. Supportive therapy will allow us to control for many of the non-specifics of therapy such as working with an empathetic provider and instilling hope and optimism. The group-nature of the supportive therapy condition will also allow us to better determine whether treatment gains were due to the content of RRT or if comparable gains can be achieved by simply increasing social connection and support via a group treatment. The supportive therapy condition will be based on existing manuals.[60] As is typical for supportive therapy conditions, the group leader will be instructed to be non-directive and allow the patients to determine the focus of each session.[61] The group leader will be encouraged to use reflective listening, elicit and validate affect, and offer empathic comments. Group leaders will also be instructed to avoid any cognitive and behavioral techniques that could overlap with RRT.

D.4. Treatment facility, clinicians, training, supervision, competence and fidelity. All treatment for the study will be provided by clinicians from the WELL Center Clinic (see Facilities for more details), an outpatient community clinic serving the Philadelphia metropolitan area. Weekly clinical supervision will be provided throughout treatment by Dr. Srivastava who will remain unblinded to allow her to provide clinical supervision. To maximize fidelity, we will use treatment manual which are designed for easy use during group treatment sessions. All treatment groups will be audio recorded, and an independent evaluator (a doctoral student with intensive training) will independently monitor and rate treatment competence and fidelity for 25% of group sessions for both conditions.

D.5. Remote study procedures. Study assessments and group therapy sessions will be conducted using an encrypted HIPAA-compliant version of Zoom videoconferencing software which we are currently using in several NIH-funded clinical trials during the stay-at-home orders. Informed consent will be collected using an electronic consent form that participants will be asked to complete during the appointment after reviewing the consent form jointly with a staff member.

D.6. Assessments. Assessments will be conducted by blinded assessors at baseline, mid-treatment (after session 5), post-treatment (after session 10), and at a 3-month follow-up. Our assessment strategy was specifically designed to allow for remote assessment during the COVID-19 pandemic and thus will only include measures that can be completed using videoconferencing or via the participants home computer. In order to maximize assessment completion, we will increase compensation across assessments ($50, $75, $100, $125).

D.6.1. Feasibility and Acceptability. Assessment of feasibility will include % of eligible patients enrolled, attrition, and study retention. We will use a Feedback Questionnaire (FQ) to obtain qualitative acceptability ratings, which will be modified from FQs used in our prior intervention development projects.

D.6.2. Primary outcomes. The Eating Disorder Examination[62] is a widely utilized, semi-structured interview for the assessment of eating disorder symptoms. We will use *number of binge episodes in the last 28 days* and *EDE global scores* as the primary outcomes. *Remission status* will also be evaluated at each assessment following the baseline assessment and will be defined as the absence of any binge episodes or compensatory behaviors in the 28 days prior to the assessment point and an EDE global score within 1 standard deviation of the community norm (EDE global <1.74).[50]

D.6.3. Secondary outcomes. We chose to use commonly-used and well-validated measures of depression (Beck Depression Inventory-II[63]), substance use (Alcohol, Smoking, and Substance Involvement Screening Test[64]), and quality of life (Quality of Life Inventory[65]) to assess secondary outcome measures.

D.6.4. Target engagement. We chose to use the same measures of target engagement that we used in our pilot trial to determine whether our pilot results will replicate when compared to a more stringent control condition. We will use the Power of Food Scale (PFS)[66] to assess reward response to palatable foods, and the Temporal Experience of Pleasure Scale (TEPS)[67] and Dimensional Anhedonia Rating Scale[68] to measure anticipatory and consummatory experiences of pleasure to day-to-day life activities. Additionally, we will also include measures of social support, companionship and social distress from the NIH Toolbox Social Relationship Scales Assessment Battery[69] to better assess the impact of RRT on social isolation and loneliness as additional targets.

D.7. Statistical analyses. A full description of the statistical analyses and power considerations can be found in the clinical trial supplement document *Statistical Design and Power.*

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