Development and Pilot Testing of a Cognitive-Behavioral Therapy-Guided Self-Help Mobile App for the Post-Acute Treatment of Anorexia Nervosa

Study 2

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1. A. List of Abbreviations

AN	Anorexia Nervosa
BMI	Body Mass Index
CBT	Cognitive Behavioral Therapy
CBT-E	Enhanced CBT for Eating Disorders
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ED	Eating Disorder
mHealth	Mobile Health
PAU	Palo Alto University
SB-ED	StudentBodies-Eating Disorders
SSCM	Specialist Supportive Clinical Management
TAU	Treatment As Usual
WUSM	Washington University School of Medicine

B. B. Introduction

B1. Study Abstract

AN is a costly and life-threatening illness that affects 1-4% of women in their lifetime.[1-4] Patients with severe AN are often treated in the acute setting, but 31-52% of patients relapse after treatment.[5-7] CBT is useful with this population, including following discharge,[10-13] and may aid in addressing psychological symptoms, achieving full recovery[9] and decreasing relapse.[14] However, very few patients have access to providers trained in these techniques.[15,16] Our team has successfully developed a guided self-help CBT-based mobile app, SB-ED, which has demonstrated effectiveness among college women with binge/purge-type EDs.[18] At the same time, we have demonstrated support for in-person CBT for the post-acute care and relapse prevention of adult AN.[11,19] Further, a recent review on digital mental health aftercare suggests this is may be feasible for maintaining treatment gains, including for EDs, but more data are needed.[17] This study, conducted at WUSM and PAU, thus proposes to test a CBT-based, coached mobile app to address the post-acute care and relapse prevention of AN.

B2. Primary Hypothesis

Study 2: Generate pilot data on feasibility and effectiveness of the mobile intervention versus the mobile intervention plus social networking versus TAU. Of note, all participants assigned to the mobile intervention conditions will also be able to access other usual care options.

Hypothesis 1: The mobile intervention plus social networking will be most successful in reducing ED psychopathology (primary outcome), reducing ED behaviors, achieving weight maintenance, reducing depression and suicidal ideation, and reducing clinical impairment.

Hypothesis 2: The mobile intervention will significantly change targets (i.e.,

reduced dietary restraint and weight/shape concerns and increased motivation to recover), more so than TAU resulting in greater clinical benefit (i.e., reduced ED symptoms).

C. C. Background

C1. Rationale for this Study

AN is a highly debilitating, costly, and life-threatening psychiatric disorder that affects up to 4% of women in their lifetime.[1,2] Mortality is extremely high, with a meta-analysis indicating the weighted mortality rate (i.e., deaths per 1000 person-years) is 5.1—this represents a six-fold increase compared to the general population and is one of the highest mortality rates of any psychiatric disorder.[22] The costs of EDs, including AN, are also staggering—in 2018-2019, the cost of EDs in the U.S. was $65 billion, equating to $11,808 per person with an ED; the additional loss of well-being per year is valued at $327 billion.[23]

Patients with severe AN are often treated in the acute setting (e.g., inpatient or other intense program), but 31-52% of patients relapse after treatment, with the greatest risk of relapse being in the months immediately following discharge.[5-7] Further, the initial goal and/or discharge criteria of these programs is typically weight restoration.[8] However, research has indicated that weight-based recovery is not "enough" and that full recovery from an ED should be defined based on physical (i.e., no longer underweight), behavioral (i.e., lack of engagement with ED behaviors), and psychological (e.g., normative levels of weight/shape concern) criteria.[9, 24-28] In the U.S., available data suggest the length of stay for patients with AN in inpatient treatment is 16-34 days and 52 days for residential.[29-31] Given that durations of 3-6 months have been recommended for recovery definitions,[9,32] it is simply not possible for individuals to achieve "recovery" during acute care, and as noted, relapse after treatment is common.[5-7] It is also during the post-acute period that individuals with AN may be more physically and cognitively capable of engaging in approaches targeting psychological symptoms, which could ultimately aid them in achieving full recovery, but problematically, the vast majority of patients do not have access to high-quality outpatient providers that could help them achieve such a goal. When individuals with EDs receive care, it is typically not an evidence-based approach, highlighting a wide research-practice gap.[15,16] The number of ED specialists who report adhering to evidence- based protocols is 6-35%, with far more therapists using an eclectic approach.[33,34] Even when therapists say they are using an evidence-based protocol, they omit crucial elements.[34,35] These factors highlight the critical need for a new model of treatment delivery to support individuals with AN in the post-acute intervention period, which has been highlighted as a key unmet need in the management of AN.[36]

C2. Prior Literature and Studies

C2.A. High potential for CBT-based mobile app

mHealth technologies have great potential to exponentially increase access to high-quality services for the post-acute treatment of AN by addressing barriers to treatment (e.g., lack of providers, logistical barriers to treatment), but to date,

research on these approaches, as well as use in the real-world, have been extremely limited. However, there is strong reason to believe a CBT-based mobile app for the post-acute intervention of AN could be successful.

First, our team has successfully developed a guided self-help CBT-based mobile app, SB-ED, which has demonstrated effectiveness among 690 college women with binge/purge-type EDs.[18,37,38] Results showed there was a significantly greater reduction in ED psychopathology in the intervention vs. control (referral to usual care on the student's campus) at post-intervention (d=-.40; p<.001) as well as over the 2-year follow-up (d=-.35; p<.001).[18] Further, 83% of intervention participants began intervention, while only 28% in control sought treatment for their ED over two years (OR=12.36; p<.001), suggesting the digital approach greatly increased realized treatment access. Grounded in CBT, our app targets core ED pathology (i.e., dietary restraint, weight/shape concerns). Key features are designed to maximize engagement and effectiveness; the app: 1) is delivered in brief, interactive sessions; 2) is "front-loaded" to address key targets early; and 3) offers personalized coaching through asynchronous messaging. Meta-analyses and reviews also support the use of digital CBT approaches for the treatment and relapse prevention of EDs.[39-41]

Second, research supports the use of in-person CBT in the post-acute treatment of AN. Our team randomly assigned 33 patients with AN to one year of outpatient CBT or nutritional counseling following hospitalization. CBT was significantly more effective than nutritional counseling.[11] Those receiving nutritional counseling relapsed significantly earlier (p<.004) and at a higher rate than the CBT group (53% vs. 22%). The overall treatment failure rate (i.e., relapse and drop out combined) was also significantly lower for CBT (22%) vs. nutritional counseling (73%) (p<.003). The CBT approach used in this study, first focused on enhancing motivation for treatment and recovery from AN, a particular challenge in this population as individuals often feel ambivalent about recovery.[42] This is also especially important given that treatment dropout rates are high for those with AN—in outpatient treatment, rates as high as 73% have been observed[43]—and meta-analyses have indicated low motivation is a major contributor to ED treatment dropout.[44] As such, motivation is critical to address as a first step in treatment for AN. Next, the treatment addressed cognitive and behavioral features associated with the maintenance of eating pathology, in addition to using a schema-based approach to address issues such as self-esteem, self-schema, and interpersonal functioning.[11] Addressing these issues could foster de-identification from the ED, a sense of purpose outside the ED, empowerment, self-compassion, and hope in recovery, oneself, and a better future, all of which have been shown in a systematic review to be critical to recovery from an ED.[21] We note that Carter et al.[45] provided further evidence that CBT may be helpful in improving outcomes for AN following intensive treatment: time to relapse was significantly longer in those randomized to CBT vs. TAU. Further, at 1-year follow-up, 65% of the CBT group and 34% of the TAU group had not relapsed.[45]

Other work has also supported the use of CBT in the outpatient treatment of

AN.[10] Specifically, Byrne et al. randomized 120 individuals with AN to one of three treatments: SSCM, MANTRA, or CBT-E.[12] There were no differences between treatments on continuous outcomes: all resulted in significant improvements in BMI, ED psychopathology, general psychopathology, and psychosocial impairment that were maintained over 12-month follow-up. There were also no differences between treatments on achievement of a healthy weight (mean=50%) or remission (mean=28%) at 12-month follow-up. Next, Fairburn et al. offered 99 adults with AN 40 sessions of CBT-E over 40 weeks; 64% completed treatment, and in these patients, there was a substantial increase in weight (mean=7.47 kg; $p<.001$). ED features also improved markedly ($ps<.001$), and over the 60-week follow-up, there was little deterioration despite minimal additional treatment.[13]

Third, digital interventions have demonstrated some initial success in supporting the aftercare of AN, but only two digital interventions have been evaluated and there are limitations of past work. First, Fichter et al. evaluated a digital, CBT-based relapse prevention program over nine months after inpatient treatment vs. TAU in 258 women with AN in Germany.[46] In addition to online psychoeducational content, participants had access to an electronic message board, monthly moderated one-hour chat sessions, and asynchronous text-based support from a therapist. Results indicated the intervention group gained weight while the TAU group had weight loss ($d=.22$); intervention completers gained significantly more weight than participants randomized to TAU ($p<.05$).[46] In an examination of the long-term (9-month) effects of the program, results indicated most variables showed more improvement in intervention vs. TAU, although only some reached statistical significance (i.e., bulimic behavior and menstrual function; $ps<.04$); in addition, the subgroup of full completers who participated in all nine of the monthly digital intervention sessions reached a significantly ($p<.05$) higher weight compared to partial users and the control group at both end of intervention and follow- up.[47] This study thus provides some preliminary evidence that CBT for this group can be delivered digitally; however, it is not clear that the intervention focused heavily on issues extremely relevant to this population and achieving recovery, including motivation, addressing weight loss during the intervention, and social support. Second, Neumayr et al. randomized 45 women with AN in Germany to an 8-week mobile intervention (German version of “Recovery Record,” an app for self-monitoring of eating as well as ED thoughts, feelings, and behaviors) with therapist feedback as an adjunct to TAU or to TAU alone.[48] Patients reported high acceptance of the app, and non-significant small to moderate between-group effect sizes favoring the intervention regarding BMI ($d=-.24$) and overall ED psychopathology ($d=.56$) at post-intervention were found; however, there were no significant differences at 6-month follow-up.[48] The intervention is currently being tested in a larger randomized controlled trial,[49] but a limitation of the app being tested (i.e., Recovery Record) is that it is primarily an ED self-monitoring app, and users do not have access to content that it is specific to relapse prevention or that addresses unique challenges in working toward recovery this population may face.[50]

These results suggest there may be potential for a digital aftercare intervention

for AN, but there are limitations to the existing work, including: 1) to date, no digital aftercare interventions have been developed in English or tested in the U.S.—this is important given the unique treatment climate in the U.S. (e.g., large country with limited access to qualified providers in many areas, no universal healthcare); 2) use of older technology with limited sophisticated features users have come to expect (e.g., the Fichter AN digital aftercare intervention was only available via the web, with content being presented in long webpage "chapters" that were only released every 30 days);[46] and 3) even when new technology has been used (i.e., Recovery Record app), it has not included specific features for aftercare support for this group, such as helping users develop internal motivation to change, addressing weight loss during the intervention, or fostering support.[48]

On the whole, this set of findings provides indication that a digital, CBT-based intervention for the post-acute intervention of AN that specifically addresses the unique needs of this population could have extremely high potential for increasing accessibility of quality care.

C2.B. Need for social support for individuals in recovery from AN

Social support has been found to be critical to recovery from AN[21,51-54], and qualitative work has revealed that ED recovery is largely influenced by a sense of connection to self and others.[55] Patients feel more hopeful about recovery when they develop stronger emotional connections with individuals supportive of recovery, and motivation for recovery is especially fueled by supportive relationships.[55] However, many individuals working toward recovery from AN report feeling misunderstood by others, including health professionals, friends, and family,[54] and as such, peer support is especially critical for recovery.[21] Individuals with EDs report that support from others who shared similar experiences is beneficial in the form of encouragement or advice, which can lead to feeling understood, connected, and less alone[21] —critical issues to address given the high levels of social isolation often seen in individuals with EDs.[56] Further highlighting the need for peer-specific support, in a three-arm pilot randomized controlled trial comparing a peer mentorship program for individuals with EDs (as an adjunct to outpatient treatment) to social support mentorship (i.e., mentorship from an individual without history of an ED) and a waiting list, results indicated session attendance and acceptability were higher in peer vs. social support mentorship. In intent-to-treat analysis, peer mentorship showed greater reductions in body dissatisfaction and anxiety compared with both control groups, and compared with waiting list, it was associated with greater reduction in binge eating in patients with BN/BED and restriction in patients with AN.[57]

One scalable way in which individuals with AN could access social support from peers/others with similar experiences is via social media.[58] Development of positive, recovery-focused online communities is especially critical in EDs given the existence of many pro-ED online communities that serve to connect people

experiencing these problems and encourage disordered behaviors.[59] Although these sites contain many harmful aspects, users perceive social support as one of the key functions, [59,60] and desire for support, interaction with others, and connecting with others with an ED are reasons individuals report for engaging with them. [61,62] Individuals with AN who are being discharged from higher levels of care for an ED, where they were surrounded each day by peers with a shared understanding of what they were going through, may experience a high degree of isolation upon returning home. Likewise, in our own work and highly relevant to the proposed study, we explored Facebook use among those with a history of receiving treatment for an ED in a group setting (including inpatient, residential, etc.).[20] Participants reported spending up to 30 minutes per day interacting on Facebook with individuals from treatment, and positive interaction with treatment peers on Facebook was associated with less ED pathology.[20] These findings point to the importance of social support, particularly from peers, in the process of recovery from AN, including the need for a positive social networking outlet, where one could connect with others in recovery. However, support from peers also needs to be moderated given evidence that online interactions with peers with EDs can turn negative.[63-65]

D. D. Study Objectives

D1. Study Aims

Aim 1: Conduct a pilot randomized controlled trial (*N*=90) of the mobile intervention versus the mobile intervention plus social networking versus treatment as usual (TAU).

Aim1a (effectiveness): Estimate the preliminary feasibility and effectiveness of the mobile intervention versus the mobile intervention plus social networking versus TAU.

Aim 1b (targets): Examine whether the mobile intervention changes the targets (i.e., reduced dietary restraint and weight/shape concerns and increased motivation to recover), as well as whether the social networking feature increases social support and improves general social networking behavior, and whether changes in targets are associated with clinical benefit.

Aim 1c (predictors and moderators): Conduct exploratory analyses to identify within-app predictors (e.g., sessions completed) and moderators of outcome (e.g., length of illness, age, psychiatric co-occurrence).

E. E. Study Design

E1. Overview or Design Summary

Participants and Recruitment.

We will enroll 90-English-speaking adult females ≥18 years who own a mobile phone and who have recently (within the past 2 months) been discharged from intensive treatment (i.e., inpatient, residential, partial hospitalization, or intensive outpatient) for DSM-5 AN. In order to be eligible, participants must have a BMI of at least 17 and must also endorse having a physician who is monitoring their medical safety. They also must have been discharged per clinical recommendations and not against medical advice.

Participants will primarily be recruited from eating disorder treatment centers. Recruitment methods may include flyers for therapists to hand out to clients and to be hung in treatment centers, emails to potential participants upon their discharge from intensive treatment, and social media posts for treatment centers to share. The study team will be responsible for creating the flyers and social media posts, and may also create a social media account specifically for the study that advertises the study and garners interest in participation. Social media recruitment may be done through Facebook, Instagram, or Twitter, using either the account of the Center for Healthy Weight and Wellness or a new account created for the Helping HAND study. These posts will not allow any comments as to ensure participant privacy. Study information may also be posted on the Center for Healthy Weight and Wellness website to spread information about and garner interest in the study. The study team will also post on existing ED recovery social media pages, through Facebook, Instagram, Reddit, and Twitter, to spread information about the study. We will also be recruiting through ED treatment nonprofits, through them posting on social media, sending out study information through their newsletters, other such methods of increasing study exposure. Recruitment materials, including emails, social media posts, and flyers, may include a link to a short eligibility screening survey, which would contain a consent form for participants to review pertinent study-related information, and questions to confirm participants' study eligibility.

Participants may also be recruited directly from therapists or treatment centers as therapists or treatment centers may provide the study team a list of clients who are eligible for the study and their contact information. [Please see page 97-98 of the research guide, referrals must obtain permission to share contact information and names of those eligible. On the other hand, the therapists or treatment centers can provide the study team contact information without additional permission.] The therapists will be made aware that they need to receive approval from their patients to share their email address. The study team may then reach out to those on the list via email or phone to inform them of their possible participation in the study.

If eligible, participants may be invited for participation in the randomized controlled trial. If they are interested in moving forward, they will provide consent online using REDCap, and may message study staff if they have any questions before moving forward. A member of study staff will read over the completed consent form to review and sign before participants move forward to complete the baseline assessment of questionnaires online using REDCap and Qualtrics. REDCap will be used to collect the majority of the

PHI, with Qualtrics only collecting the participant's first name and last four digits of their phone number. After completion of the surveys, participants will have their first virtual visit with a study staff member so their weight can be taken. They will then be randomized to one of three study conditions: mobile intervention; mobile intervention plus social networking; or TAU. Combinations of conditions may be used to create strata for randomization, including length of illness, clinical impairment, patient health, anxiety, and age. We will randomly assign participants to groups using Qualtrics, and participants will be informed of their randomized condition following the completion of the baseline assessment.

Study Conditions

There are three study conditions to which participants could be assigned:

1) Mobile intervention condition: Participants randomized to the mobile intervention condition will receive access to our mobile app. Participants will have access to the app for 6 consecutive months.

2) Mobile intervention plus social networking condition: Participants randomized to the mobile intervention plus social networking condition will receive access to our mobile app. They will also receive access to the social network. Participants will have access to the app and social network for 6 consecutive months.

Of note, participants assigned to both conditions 1 and 2 will also be able to access other usual care options and will be encouraged to follow the discharge plan provided to them by the ED program from which they were discharged.

3) TAU condition: Participants not randomized to conditions 1 or 2 will be encouraged to follow the discharge plan provided to them by the ED program from which they were discharged. We will also encourage participants to follow up with their ED program for additional referral information as needed and/or reach out to NEDA and/or ANAD for assistance with finding treatment providers/resources as needed. NEDA and ANAD provide helplines and online treatment provider databases to help individuals find providers.

Participants in all conditions will receive an email prompt one week following baseline completion, reminding them to pursue the recommended strategies. After participants are randomized to one of the three conditions, they will receive a scale in the mail in approximately one week. The scale, shipped to the address participants provide in the Baseline Survey, is a cellular scale from the company Body Trace. The study staff will update a spreadsheet shared with Body Trace through Wustl Box.net with information about participants including their name and address. The Body Trace scales will collect scale readings and timestamps of the readings. The participants will have the choice to have the Body Trace scale display turned "on," which would display their weight measurement in pounds, or turned "off," which would not show their weight and only indicate the scale is working through showing "OK" on the scale display. Participants will choose to have the scale turned "on" or "off" for each of the weight measurement visits, baseline, 6-weeks, 6-months, 9-months, in the survey preceding the visit.

Retention

We will implement several practices to maximize retention. Participants will provide their primary and alternate phone numbers and email addresses. Reminder emails, a phone call, and text reminders may be sent over the course of 3 weeks for each assessment.

We will also obtain names and contact information for two collaterals (e.g., parent, partner, close friend) likely to know their whereabouts, who may be contacted when all attempts to locate the participant are unsuccessful. Participants will be assessed online at baseline, 6 weeks, 6 months, and 9 months post-randomization. They will receive Amazon e-gift cards of $25 for the baseline and 6-week assessments, $35 for the 6-month assessment, and $45 for the 9-month assessment. Intrinsic motivational efforts will also be used, including thank-you and study update emails.

E2. Subject Selection and Withdrawal

E2.A. Inclusion Criteria

Cisgender woman; ≥18 years old; owns mobile phone; has been discharged from intensive treatment (i.e., inpatient, residential, partial hospitalization, intensive outpatient) for DSM-5 AN within the past 2 months; English-speaking; U.S. resident; BMI ≥ 17; is medically stable.

E2. B. Exclusion Criteria

Not cisgender woman; <18 years old; does not own mobile phone; has not been discharged from intensive treatment (i.e., inpatient, residential, partial hospitalization, intensive outpatient) for DSM-5 AN within the past 2 months; BMI < 17. We are also assessing medical stability, excluding any individuals who endorse currently using a feeding tube, currently endorse chest pain, experiencing dizziness when sitting or standing, experience shortness of breath, experienced any blurred vision or dark spots in the past 24 hours, or purged 3 or more times in the last 24 hours.

E2.C. Ethical Considerations

All key personnel involved in the design or conduct of research involving human subjects will receive the required education on the protection of human research participants prior to the start of the study. Participants will be informed that they do not have to answer any questions that make them uncomfortable. There are minimal risks for participating in usability testing.

Participants will be provided with the contact information of the research staff. As a clinical psychologist, the PI is trained in how to address safety issues. If any participant appears to be in crisis during usability testing, they will be given information to call emergency services. Any adverse event will be reported promptly to the NIH and the IRB.

Confidentiality: Participant confidentiality will be maintained in compliance with

HIPAA privacy protected servers. Study IDs will be linked with participant names and email addresses in a separate password-protected file stored on a secure, password-protected server that only key study personnel have access to. All employees of the study with access to protected health information (PHI) are required to complete HIPAA training and comply with the privacy procedures in place at Washington University.

Adverse Events: For the purpose of this study, adverse events will be defined as unanticipated problems involving risks to the study participants. A serious adverse event will be defined as any untoward occurrence that results in death, is life-threatening, or creates persistent and significant disability. Any potentially adverse events will be evaluated by the PI within 72 hours.

It is important to note that in previous similar clinical trials of digital health interventions, the procedures outlined above have been used to protect against and minimize potential risks to participants, and they have proved effective in preventing emotional and physical complaints as well as adverse events.

E2. D. Participant Recruitment Plans and Consent Process

We will enroll 90-English-speaking adult cisgender women ≥18 years who own a mobile phone and who have recently (within the past 2 months) been discharged from intensive treatment (i.e., inpatient, residential, partial hospitalization, or intensive outpatient) for DSM-5 AN. In order to be eligible, participants must also be considered medical stable, including endorsing having a physician who is monitoring their medical safety, not be currently using a feeding tube, have no current chest pain, do not experience dizziness when sitting or standing, do not experience shortness of breath, have not experienced any blurred vision or dark spots in the past 24 hours, and have not purged 3 or more times in the last 24 hours, as well as having been discharged per clinical recommendations and not against medical advice. Participants will also need to have a BMI of at least 17.

Participants will primarily be recruited from eating disorder treatment centers. Recruitment methods may include flyers for therapists to hand out to clients and to be hung in treatment centers, emails to potential participants upon their discharge from intensive treatment, and social media posts for treatment centers to share. The study team will post on existing ED recovery social media pages/ group as well, to spread information about the study. We will also be recruiting through ED treatment nonprofits, through them posting on social media, sending out study information through their newsletters, other such methods of increasing study exposure. The study team will be responsible for creating the flyers and social media posts, and may also create a social media account specifically for the study that advertises the study and garners interest in participation. Recruitment materials, including secure emails, social media posts, and flyers, may include a link to a short eligibility screening survey, which would contain a

consent form for participants to review, pertinent study-related information, and questions to confirm participants' study eligibility.

Participants may also be recruited by direct referral from therapists or treatment centers. Therapists or treatment centers may provide the study team a list of clients who are eligible for the study and their contact information. Therapists will be made aware that they need to receive approval from their patients to share their email address with the research team. The study team may then reach out to those on the list via email or phone to inform them of their possible participation in the study.

E2. E. Randomization Method

If eligible, participants may be invited for participation in the randomized controlled trial. If they are interested in moving forward, they will provide consent online using REDCap, and may message study staff if they have any questions before moving forward. A member of study staff will read over the completed consent form to review and sign before participants move forward to complete the baseline assessment of questionnaires online using REDCap and Qualtrics. REDCap will be used to collect the majority of the PHI, with Qualtrics only collecting the participant's first name and last four digits of their phone number. After completion of the surveys, participants will have their first virtual visit with a study staff member so their weight can be taken. They will then be randomized to one of three study conditions: mobile intervention; mobile intervention plus social networking; or TAU. Combinations of conditions may be used to create strata for randomization, including length of illness, clinical impairment, patient health, anxiety, and age. We will randomly assign participants to groups using Qualtrics, and participants will be informed of their randomized condition following the completion of the baseline assessment. Individuals will be placed into one of three groups equally, so each condition will have 30 participants.

E2. F. Risks and Benefits

Risks:

*Physical risk*s: There are minimal physical risks of participating in this study. However, we acknowledge that this population may experience a setback in their recovery and a chance of unhealthy weight loss. Please see our risk management plan to see how we propose to monitor and address these issues.

Psychological risks: There are minimal psychological risks of participating in our proposed mobile intervention, although we recognize that programs designed to address mental health problems may promote increased focus on mental health symptoms in some individuals, more than which may exist before starting the program. However, we note that individuals who we enroll will have recent ED treatment experience and may very likely be engaged in ongoing outpatient care as well, suggesting they already have exposure to interventions that promote an

increased focus on their symptoms

Social risks: There may be some embarrassment related to completing questions related to disordered eating and its treatment.

Financial risks: N/A

Legal risks: N/A

Risks to privacy: There are minimal to no risks to participant privacy. We will go to great lengths to keep participant information private and confidential.

Other risks: N/A

Risk management:

Several safety procedures will be implemented:

1. 1. Coaches for the mobile program, hosted by SilverCloud Health, will be students in a graduate program in psychology, counseling, or social work or trained staff with a mental health background. Coaches in SilverCloud Health will be recruited from the institutions of the study team members, WUSM and PAU. Coaches will be trained in cognitive-behavioral therapy for eating disorders, motivational interviewing, risk management, and the SilverCloud platform, and will be under the close supervision of coach supervisors at WUSM and PAU, attending weekly supervision led by Dr. Fitzsimmons-Craft, who will also serve as their on-call supervisor in the case of risk situations.

2. 2. Coaches will monitor the platform at least weekly to assess for significant changes in symptoms (e.g., suicidality, increased purging, concerning weight loss). Any participant deemed unsafe or needing more intensive clinical intervention will be given a referral by their coach as well as contacted directly via telephone. Appropriate follow-up (e.g., contacting the participant's emergency contact) will be implemented if participants are deemed to be at imminent risk and no response is provided by the participant indicating their safety. This protocol is to safeguard against concerns with keeping individuals in guided self-help care when more intensive services are warranted.

3. 3. Participants will be required to endorse having a physician who is monitoring their medical safety.

4. 4. Participants in any of the study conditions who meet the clinical/subclinical

ED threshold at any follow-up assessment will be given a referral and encouraged to follow-up with or stay in care.

5. 5. Weight of participants will be monitored throughout the course of the study using a study-provided cellular scale for research purposes as well as to ensure the safety of participants. If a participant loses a significant amount of weight (defined by their coach and coach supervisor on a case-by-case basis) or reaches a BMI of 16.5, additional steps will be taken. First, the participants will be informed that their weight is trending downwards, and they will need to complete weekly weights with their coach until they gain weight to ensure their safety. If, after 3 consecutive weights, the participant is still at concerning weight, additional steps will be taken. Alternatively, if the participant reaches a BMI of 14.5, additional steps will be taken immediately. Additional steps include notifying emergency contacts that the health of the participant is in danger and more intensive intervention is recommended. The participant will be informed that they can no longer participate in the study, and they will also be given resources for seeking more intensive treatment.

6. 6. The social networking feature will be monitored daily by coaches for any inappropriate or potentially triggering content. Participants will use their personal social media accounts.

1. a. For Facebook: To mitigate the risk of participants communicating with each other without moderation, we may activate the Facebook feature that requires all posts, including edits on a post, to be approved by a moderator. In other words, no post will be published until a moderator reviews it and approves it. This will ensure that inappropriate content is not posted. Our team and coaches will serve as moderators and will review and approve content at least once every weekday, to ensure that posts are reviewed and approved in a timely manner. Because of the nature of Facebook, study participants could theoretically send friend requests to each other within the platform and exchange privately; however, this would be similar to people befriending each other in a treatment setting and exchanging privately in some way (e.g, via social media, text messaging).

2. b. For Instagram: The Instagram page will be monitored at least once daily by the study team to verify that no at-risk (i.e., mentions plans to harm self or others) or inappropriate (e.g., bullying, ED triggering text, other explicit content) comments are shared. If any of these types of comments are shared, the moderator will consult with the supervisor and the user's coach and will remove this comment. If the comment is removed but is unrelated to risk, a short note regarding the social networking community guidelines can be included in the user's next review. If the comment mentions a plan to harm one's self or others, the supervisor will work with the coach moderator to remove this comment and send the participant an email with the national crisis helplines and resources. Direct messages are intentionally closed to prevent risk situations from being disclosed in this forum. Community Guidelines for the social networking feature will be listed and pinned in the Instagram Story Highlights. By commenting, participants agree to adhere to these guidelines and are aware that comments not meeting these may be removed.

1. 7. In the case of imminent risk, such as in the extremely rare case of a user reporting plans of suicide or homicide, there are several steps that coaches are mandated to take as mandated reporters. Coaches may identify the appropriate local agency such as the police to prepare for possibly making a report. They may provide the user with a variety of

emergency options such as the suicide hotline phone number, an emergency room location, or local police information and encourage clients to seek additional support or hospitalization through these options. Furthermore, coaches may gather relevant information by reviewing the coaching record for all identifying information available such as name, age, phone number, address, and email address to provide to the agency when making a report. If it is deemed appropriate by the coaching supervisor, coaches may call in the report as soon as possible to the identified local agency. They may also follow up with the user, express concern, provide support, and let him/her know a report has been made. In addition, coaches may follow up with the coach supervisor via email to let them know the report was made, and may also follow up with the emergency contact the participant provided at the start of the study. Finally, coaches may continue to monitor the user for emerging or worsening risks, as demonstrated by information the user inputs into the program or messages to the coach, and they continue to keep in close contact with the coaching supervisor. Should the user continue to worsen and be deemed at continued imminent risk, the coach and coach supervisor may make a decision to withdraw the participant from the program.

7. If a participant endorses self-harm in a survey, they will automatically receive information about how to contact the suicide prevention hotline at the end of the survey. Those not eligible for the study and participants in the control group will receive information about how to contact the National Eating Disorder Association (NEDA) Helpline and how to access other resources on the NEDA website.

Potential benefits

The benefits to participants in this study and to society are expected to be great. In terms of potential benefits to participants, these include: reduced ED, anxiety, and/or depressive symptoms, improved quality of life, and decreased risk of relapse or need for future acute treatment. In addition, it is possible that skills to solve ongoing problems that may maintain mental health problems may improve. Therefore, the potential risks that are associated with this study are reasonable when considering the many benefits that the participants and society may gain and the fact that currently 50% of individuals with anorexia nervosa relapse after acute treatment.

Importance of the Knowledge to be Gained: Achieving our aims will provide key data on the potential for a CBT-based mobile app to support individuals in the post-acute treatment of AN—a population for which there has been extremely limited treatment options to date, let alone ones that are accessible throughout all parts of the U.S. and anytime. Should this approach ultimately demonstrate success, not only could acute settings across the U.S. refer their patients with AN to this program, but individuals with AN without access to other care options could access the program directly, such as through a referral from ED non-profits, including the National Eating Disorders Association (NEDA), Project HEAL, or the National Association of Anorexia Nervosa and Associated Disorders (ANAD).

E2. G. Early Withdrawal of Subjects

Informed consent will make clear that participants may withdraw at any time with

no penalty.

E2. H. When and How to Withdraw Participants

Taking part in this research study is voluntary. Participants may choose not to take part in this research study or may withdraw their consent at any time. They may withdraw by telling the research team they are no longer interested in participating in the study or they may send in a withdrawal letter. There will be no penalty or loss of benefits to which they were otherwise entitled.

E2. I. Data Collection and Follow-up for Withdrawn Subjects

When a participant withdraws from the study, the research team will stop collecting data from them.

1. F. Study Procedures

F1. Screening for Eligibility

People interested in participating in our study may follow a link to our online screen or may complete the screen over the phone with a study team member. They will be asked to review the consent form (if on the phone a team member will go over the consent form with them). The eligibility screening survey may ask respondents their treatment history, eligibility questions (own smartphone, height and weight, age, being under the care of a physician) and demographic questions.

F2. Schedule of Measurements

Participants will be assessed at baseline, 6 weeks, 6 months, and 9 months. All surveys will be administered via REDCap and Qualtrics. REDCap will be used to collect most of the PHI and Qualtrics will only collect the participant's first name and last four digits of their phone number. Participants will be compensated by receiving an electronic gift card for completing the Baseline ($25), 6 week ($25), 6 month ($35), and 9 month ($45) follow-up assessments. See the table below for the schedule of assessments. In the mobile app group, participants will be given access to the Helping HAND app for 6 months and be able to access this app and utilize the coach at their convenience. In the mobile app plus social media group, participants will also be given access to the Helping HAND app and coach, as well as to a private monitored social media page to interact with others in that condition.

F3. Data Collection and Reporting Procedures

Because the online interventions follow standard practice guidelines that have been used in research trials without significant adverse events, we do not

anticipate any significant adverse events. However, coaches will be trained to monitor for adverse events, including Serious Adverse Events (SAEs) such as deaths, hospitalizations, and life threatening events and Unanticipated Problems (UPs), and will report any potential adverse events immediately upon their identification. We will also monitor for adverse events at all follow-up assessments and via all other communication with study participants.

To ensure participant safety, any potentially adverse events will be monitored. An event that meets the definition of an unanticipated problem involving risk to participants or others and results in the death of participants will be reported to the IRB at Washington University within 1 day and to the NIMH within 5 days. An event that meets the definition of an unanticipated problem involving risk to participants or others and does not result in the death of participants will be reported to the IRB at Washington University and to the NIH within 10 working days. Adverse Events and Serious Adverse Events, as described above, that do not also meet the definition of an unanticipated problem involving risks to participants or others will be reported to the IRB at Washington University upon continuing review and to the NIMH upon the annual progress report. Unexpected Adverse Drug Events that result in the death of a participant will be reported to the IRB at Washington University within 1 day and to the NIMH within 5 days. Unexpected Adverse Drug Events that do not result in the death of a participant will be reported to the IRB at Washington University and to the NIH within 10 working days.

F4. Study Outcome Measurements and Ascertainment

This study will generate pilot data on feasibility and effectiveness of the mobile intervention versus the mobile intervention plus social networking versus TAU. Of note, all participants assigned to the mobile intervention conditions will also be able to access other usual care options. Study outcomes include the following:

Reduced ED psychopathology (e.g., dietary restraint, weight/shape concerns, obsessive compulsive personality traits)

Increased motivation to recover

Increased social support, decreased engagement with ED promoting social media, and interaction with the study specific social media page

1. G. Statistical Plan

G1. Sample Size Determination and Power

The primary purpose of an R34 is to test the feasibility and acceptability of an intervention and is not intended to be powered to detect a predicted effect size. Thus, our small pilot RCT (total N=90) is intended to test the feasibility and acceptability of engaging participants with the mobile intervention/social networking component and to estimate its preliminary effectiveness on ED psychopathology and other secondary outcomes, as well as whether it engages the targets. Nevertheless, we have examined power, and a sample of n=30 per

group will provide 28% power when the true EDE-Q Global between-group mean difference is 0.5 and 80% power when the difference is 1.05. Power is thus reasonable for this pilot R34, which is intended to show feasibility, acceptability, and to inform the design of a larger randomized controlled trial study for confirming our findings.

G2. Interim Monitoring and Early Stopping

The DSMB will provide oversight and ongoing monitoring of participant safety, quality of data collection, and integrity of the study on a yearly basis. The DSMB will receive a report from the study team approximately two weeks before each review date. These reports will include the major variables necessary for monitoring safety, quality of data collection, and integrity of the study and will include otherwise blinded outcome data. The DSMB will prepare a report after every meeting based on the material received, which will be forwarded to the PI and also forwarded to the IRB by Dr. Fitzsimmons-Craft.

G3. Analysis Plan

Aim 1 (effectiveness): All analyses will be intention-to-treat (ITT) analyses, and the principal strategy to examine primary and secondary outcomes over time between the groups (i.e., mobile intervention, mobile intervention plus social networking, TAU) will be the use of mixed random effect repeated measures models, with participant as a random effect and with treatment group, time, and treatment by time interaction as fixed effects. Use of other treatment will be assessed and modeled as a covariate to control for differences in the amount of other treatment between participants. Linear mixed models will be used to compare ED psychopathology (primary outcome), BMI, depression, suicidal ideation, and clinical impairment. For frequencies of ED behaviors, we will use a generalized linear mixed model with a log link, and for rehospitalization and full recovery rates (binary outcomes), we will use a logit link. These models will allow us to test whether intervention effects in outcomes are observed at 6 months (i.e., end of intervention period) and whether the obtained effects are sustained during subsequent follow-up at 9 months (i.e., 3 months after the intervention period). Effect sizes and 95% confidence intervals will be reported.

Aim 2 (targets): We will use moderated mediation analysis to examine whether clinical targets affect our outcomes of interest (particularly our primary outcome, ED psychopathology), and whether these effects differ by intervention group. We will test for mediation using structural equation models (SEM) with confidence intervals derived from bootstrapping of indirect and total effects. By applying moderated mediation analyses, we will be simultaneously testing whether the intervention engages the targets and whether intervention-induced changes in targets are associated with clinical benefit.

Aim 3 (predictors and moderators): Potential moderators (i.e., length of illness, impairment, psychiatric comorbidity, age) will be examined using interaction terms with intervention group assignment in models described above to identify subgroups that benefit most from the intervention (with or without the social networking feature) and others for whom additional tailoring may be necessary in

future refinements of the app. Assessment of within-app treatment predictors will use the models described in the analyses for Aim 2a but will include each predictor represented as a covariate and predictor by time interaction.

We note that due to our small sample size for this pilot and feasibility study, we will focus on effect sizes for outcomes and targets rather than statistical significance in all of the above-mentioned analyses in order to inform sample size/power calculations as well as necessary subgroup analyses for a future larger trial.

G4. Missing Outcome Data

All analyses will be intent-to-treat analyses, using full-information maximum likelihood to handle missing data.

1. H. Study Monitoring, Auditing, and Inspecting

H1. Study Monitoring Plan: Data Safety and Monitoring Board (DSMB)

An independent panel of experts with experience in clinical trials, biostatistics, and EDs, consisting of three members who are not affiliated with the study – including an intervention researcher, a biostatistician, and a patient advocate – will be appointed to constitute a Data Safety and Monitoring Board (DSMB). Members will be named prior to the commencement of participant enrollment. In addition, the study PI (Dr. Fitzsimmons-Craft) and designated staff will attend the DSMB meetings (as non-voting participants) and will be responsible for preparing and presenting data reports from the study. The DSMB will provide oversight and ongoing monitoring of participant safety, quality of data collection, and integrity of the study on a yearly basis. The DSMB will receive a report approximately two weeks before each review date. These reports will include the major variables necessary for monitoring safety, quality of data collection, and integrity of the study and will include otherwise blinded outcome data. The DSMB will prepare a report after every meeting based on the material received, which will be forwarded to the PI and also forwarded to the IRB by Dr. Fitzsimmons-Craft.

The DSMB will provide the following functions:

Review of data (including masked data) over the course of the trial relating to efficacy, recruitment, randomization, adherence, retention, operating procedures, forms completion, intervention effects, ethnic/racial minority inclusion, and participant safety.

Identification of problems relating to safety over the course of the study. The study PI will be informed by phone and via written report of their findings and recommendations.

Identification of needs for additional data relevant to safety issues and request of these data from the study investigators.

Selection of appropriate analyses and periodic review of data on safety and outcomes.

Recommendations regarding recruitment, treatment effects, adherence, retention, safety issues, and continuation of the study.

Provision of written reports to the Project Officer and the PI following each DSMB meeting. These reports will summarize the key issues reviewed by the DSMB.

The frequency and type of data review is summarized in the following table, with additional information following:

Data	Review Frequency
Participant accrual (with demographic data)	Semiannually
Adverse events	Within 72 hours
Adverse and other events review	Annually
Intervention compliance	Annually
Discontinuation rules report regarding statistical power implications of drop-outs and missing data	Annually

1. I. Data Handling and Record Keeping

Data will be stored on HIPAA privacy protected servers at Washington University in St Louis. Only the PI and designated research staff will have access to individually identifiable private information about human subjects. All research materials collected will be identified only by a code number and will be stripped of individually identifiable private information. Only the PI and designated research staff will have access to the key.

SilverCloud Health is a HIPAA-compliant digital health company. SilverCloud Health will host the proposed program and all data collected within the program. Prior to beginning this study, SilverCloud Health and Washington University will enter into a Business Associate and Qualified Service Organization agreement. SilverCloud Health will comply with the rules on handling of Protected Health Information under HIPAA.

H1. Confidentiality and Security

Our products and services are offered through public and private networks. There are a wide range of tiered controls to ensure the appropriate level of protection to systems and data in transit. Vulnerability scanning of our internet-facing sites is undertaken regularly and policy compliance software is used to ensure systems are maintained in accordance with security requirements. Penetration testing companies are engaged to provide a further level of assurance. Malware/ malicious code - In accordance with industry practices, Washington University - School of Medicine utilizes many techniques to protect its IT systems from malicious software and other attacks. Prime examples include: - Alerting –

Security alerts for new threats are received from a variety of sources including software vendors and CERT organizations. These alerts are evaluated by security specialists and circulated across the company with instructions on mitigating actions. - Protection – Protection measures include the application of patches, hotfixes, and other configuration workarounds that have been recommended by software vendors. Other methods of protection include the use of anti-virus software, filters and intrusion detection. Firewall filters to block outbound communication to known malware command and control servers. - Controls – The service delivery of many Washington University - School of Medicine products relies on Personal Computers (PCs) as the main interface to customers. Where specialized software is supplied to allow the PC to run as a 'Washington University - School of Medicine Desktop', rigorous controls are applied at all stages of development, testing and software distribution of the code to prevent viruses, 'trojan horses' or other malicious code.

All major Data Centers meet Washington University - School of Medicine Corporate Technical Policy guidelines. The University's guidelines include requirements for physical security, building maintenance, fire suppression, air conditioning, UPS with generator back-up, and access to diversely delivered power and communications. Periodic audits and reviews are conducted that determine the recovery level of the site. A variety of methods are used to control access to Washington University - School of Medicine sites and depending on the sensitivity of the facility, may include some or all of the following: the use of security staff, ID cards, electronic access control systems incorporating proximity card readers, pin numbers or biometric devices. Monitoring and audit - Automated and systematic checking of systems, services and operations are undertaken to ensure compliance with policy, and effectiveness of applied security controls. Network management, Intrusion Detection, SIEM and other security tools are also implemented and operationally managed to monitor and maintain a highly secure systems environment. The Internal Audit department functions independently from all Operations and Development activities. The department gives advice and assurance on the controls within Washington University - School of Medicine production systems. Its staff includes both professionally-qualified auditors and staff with specific technology backgrounds. Privacy/data protection compliance program - The Washington University - School of Medicine respects privacy and seeks to protect personal data in accordance with its privacy policy. The university's privacy and security policies cover areas such as access control, authentication, audit, monitoring, data storage and backup, and transmission standards.

1. J. Study Administration

Dr. Fitzsimmons-Craft (PI), as well as Co-Is Drs. Wilfley, Taylor, and Pike, will be members of the Study Executive Committee (SEC). While the PI will be primarily responsible for decision-making related to the overall scientific conduct of the study and monitoring the overall study progress to ensure its timely completion, the Co-Is will assist in this process. The SEC will be responsible for final approval of the study protocol and any changes to the protocol, all of which will be documented in writing as part of the

SEC meeting minutes. Dr. Fitzsimmons-Craft is the PI and will direct the Clinical Coordinating Center (CCC), with support from Co-I Dr. Wilfley. The CCC will be responsible for study oversight, including participant recruitment, coordination and monitoring of study procedures and progress, liaising with SilverCloud, the study's Technology Partner, and collection of data.

J1. Funding Source and Conflicts of Interest

This study is funded by R34 MH127203. There are no relevant conflicts of interest to report.

J2. Participant Payment

Participants will be compensated by receiving an electronic gift card for completing the Baseline ($25), 6 week ($25), 6 month ($35), and 9 month ($45) follow-up assessments. See the table above for the schedule of assessments.

J3. Study Timeline

As detailed in the table below, recruitment and enrollment for the pilot randomized controlled trial will begin in Year 2. It is anticipated that enrollment will continue for one year. For those randomized to the mobile intervention (with or without the social networking component), they will receive access for 6 months. Participants will complete a baseline assessment, as well as assessments at 6 weeks, 6 months, and 9 months (which will thus occur 3 months after access to the mobile intervention has ceased). Thus, it is anticipated that data collection will be complete about 9 months into Year 3, allowing time in the final months of the grant to finalize data analysis and write findings up for publication.

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