DOCUMENT:

INFORMED CONSENT AND ASSENT

OFFICIAL STUDY TITLE:

TREATMENTS FOR IMPROVING MOOD IN DEPRESSED TEENS

(TEEN THRIVE-3)

R34AT009886

NCT NUMBER:

NCT03831360

DOCUMENT DATE:

(12/10/2020)

Clinical Intervention Study Protocol

TREATMENTS FOR IMPROVING MOOD IN DEPRESSED TEENS

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Supported by:

The National Center for Complementary and Integrative Health, R34AT009886

Tool Revision History

Version Number: 1.1
Version Date: 9/14/2018
Summary of Revisions Made: N/A

Version Number: 1.2
Version Date: 9/24/2018
Summary of Revisions Made: specified that Phase 1 focus groups may include as few as one adolescent/parent for scheduling or other reasons.

Version Number 1.3
Version date: 11/14/2018
Summary of Revisions Made: removed the exclusion criteria that stated that participants may not be enrolled in CBT for Phase 1 focus groups. Removed the Psychotherapy Practice Scale-Patient Depression Care Version from the set of screening questions and added a modified version to the demographics page.

Version Number 1.4
Version date: 12/3/2018
Summary of Revisions Made: minor modifications to exclusion criteria for Phase 2 and 3; changes to assessment instruments used including substitution of MINI for K-SADS; specified that the BL2 time point is conducted by phone and will not include QIDS administration; clarified timing of phone screen, BL1, BL2, and enrollment; clarified how protocol deviations and quality management will be recorded

Version Number 1.5
Version date: 1/3/2019
Summary of Revisions Made: clarifications requested by NCCIH; minor errors corrected

Version Number 1.6
Version date: 2/4/2019
Summary of revisions made: added language about identification and reporting of protocol deviations

Version Number 1.7
Version date: 3/27/2019
Summary of revisions made: changed the total number of participants allowed per class to be 12; modified inclusion criteria; specified injuries due to yoga should be assessed weekly in teens only

Version Number 2.0
Version date: 7/29/2019
Summary of revisions made: Specified that class is approximately 45 minutes long; Changed the manual that used to guide group CBT; Specified that we will exclude adolescents with a history of a manic episode (but not exclude adolescents with a possible history of a hypomanic episode); expanded recruitment options; Clarified that we may ask the adolescent screening questions by phone prior to talking with the parent; Stated that all participants must meet listed

requirements for inclusion at the phone screen stage in order to have a Baseline 1 (BL1) visit scheduled; Revised the language for how we will discuss homework in the yoga classes; Changed the assessment schedule to include two MINI modules (mania/ hypomania, and suicidality) at M3, M6, and M9; Specified that PHI may be included in a REDCap database that is designated for PHI.

Version Number 2.1.
Version date: 12/5/2019
Summary of revisions made: we added a brief assessment of teen treatment arm preference at baseline.

Version Number 2.2.
Version date: 12/18/2019
We revised inclusion criteria to include, in Phase 3/ study A, participants with QIDS >= 10 and with suicide ideation if it is currently being treated.

Version Number 2.3.
Version date: 2/12/2020
We revised procedures so that, in Phase 3, in order to be invited for a baseline visit, teens must score an 8 (rather than 5) or greater on the PHQ-8 on the telephone screen.

Version Number 2.4.
Version date: 3/13/2020
We made provisions for being able to conduct interventions via audio/ videoconferencing should we be unable to hold in-person classes due to COVID-19.

Version Number 2.5.
Version date: 3/20/2020.
Further clarifications regarding risks and benefits of holding classes via videoconference.

Version Number 2.6.
Version date: 3/26/2020
Clarified options for paying participants, and that we would send them REDCap link to be able to view a written version of the oral consent for videoconference.

Version Number 3.0.
Version date: 5/1/2020
Updated protocol to allow for remote recruitment and video-based baseline visit.

Version Number 3.1.
Version date: 10/29/2020.
Clarified inclusion / exclusion criteria for passive vs. active suicide ideation.

Version Number 3.2.
Version date: 12/10/2020
Changed follow-up duration to 6 months.

TABLE OF CONTENTS

Page

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PRÉCIS

Study Title

Treatments for improving mood in depressed teens

Objectives

Our proposed project will have three phases. Specific Aims for each phase include:

Phase 1: Initial Development

1. Conduct separate focus groups with depressed adolescents (n=24) and parents (n=24) to ascertain their feedback on ways to make yoga classes an acceptable and feasible intervention;
2. Solicit feedback from experts in depression, health, and/or yoga in adolescents;
3. Create a manual, training materials, and fidelity assessment scale for instructors.

Phase 2: Open Trial

4. Pilot the 3 month yoga intervention in a sample of 12 adolescents;
5. Via structured interview, elicit feedback from adolescents, parents, and yoga instructors; use the feedback to further refine the yoga manual and other related materials.

Phase 3: Pilot RCT (Study A)

6. Conduct a pilot randomized clinical trial (n = 34) of 3 months of hatha yoga vs. group CBT for depression for adolescents aged 13-18 with major depression; we also refer to this as Study A. [Note. There will also be a Study B in which we may enroll up to an additional 20 adolescents that do not meet Phase 3 (Study A) inclusion criteria due to either low depression severity on the QIDS or recent changes in treatment. Study B will run concurrent to Phase 3/Study A. Participants will undergo the same procedures as the main Phase 3 participants. Allowing these individuals to participate will allow us to increase the size of the yoga/ CBT classes, potentially making them of more value for all participants.]
7. Assess feasibility, acceptability, and safety of both the yoga intervention and comparison group;
8. Assess within-group changes on outcomes. The primary outcome will be adolescent report of depression symptom severity at 3 months, assessed by a blind evaluator. Secondary outcomes include depression severity at follow-up (9 months), and self-report of depression, functional impairment, and anxiety at 3 and 9 months.

Thus, our primary objective for this pilot project is to develop procedures, and manuals, and acquire supportive data on feasibility and acceptability that will prepare us to conduct a fully-powered non-inferiority design trial of hatha yoga vs. group CBT for depression in adolescents.

Design and Outcomes

In Phase 1, we will conduct focus groups with adolescents with depression, with separate but concurrent focus groups for their parents.

In Phase 2, we will conduct an open single-arm pilot trial of our adapted hatha yoga to examine feasibility, acceptability, and safety, and to gather additional feedback from adolescents, parents, and yoga providers to guide further refinement of the manual. Participants will be

adolescents with depression. Parents will also be invited to participate in assessments regarding their child, although it is not required.

In Phase 3, Study A, we will conduct a pilot RCT of hatha yoga vs. group CBT to assess feasibility, acceptability, and safety of these interventions, examine preliminary outcomes of depression, functional impairment, and anxiety, as well as engagement of hypothesized mechanisms of self-compassion, and metacognitive awareness. Participants will be adolescents with depression. Parents will also be invited to participate in assessments regarding their child.

Study B, which will run concurrent to Phase 3, will be for participants who did not meet the depression inclusion criteria or had recent changes in therapy or medications that make them ineligible for Phase 3. Participants will be randomized to Phase 3 groups of hatha yoga or group CBT. Parents will also be invited to participate in assessments regarding their child.

Interventions and Duration

Yoga classes. The manualized hatha yoga program will begin with a 20-minute initial individual session with a yoga teacher, to introduce the participant to yoga and give them a chance to privately ask any questions or express any concerns. Subsequently, participants will be asked to attend one class (approximately 45 mins long) per week for 12 weeks. Participants in Phase 2 will participate for 3 months. Participants in Phase 3 will participate for 6 or 9 months (12 weeks of intervention, 3 or 6 months of follow up).

Phase 3 only - Group CBT. We will provide group CBT for depression.. Participants will attend group sessions for 12 weeks. Participants in Phase 3 will participate for 6 or 9 months (12 weeks of intervention, 3 or 6 months of follow up).

Sample Size and Population

The proposed project will include up to 24 depressed adolescents and 24 parents who participate in focus groups (Phase 1), 12 adolescents in an open trial (Phase 2; also including 12 parents), 34 human subjects in a randomized controlled trial of yoga vs. group Cognitive Behavioral Therapy (CBT) (Phase 3; also including 34 parents), and up to 20 adolescents in Study B (and up to 20 parents). Participants will be adolescents aged 13-18 years old, regardless of gender.

1. STUDY OBJECTIVES

1.1 Primary Objective

Our primary overall objective for this pilot project is to develop procedures and manuals, and acquire supportive data on feasibility and acceptability that will prepare us to conduct a fully-powered non-inferiority design trial of hatha yoga vs. group CBT for depression in adolescents.

Our proposed project will have three phases. Specific Aims for each phase include:

Phase 1: Initial Development

1. Conduct separate focus groups with depressed adolescents (n=24) and parents (n=24) to ascertain their feedback on ways to make yoga classes an acceptable and feasible intervention;
2. Solicit feedback from experts in depression, health, and/or yoga in adolescents;
3. Create a manual, training materials, and fidelity assessment scale for instructors.

Phase 2: Open Trial

4. Pilot the yoga intervention in a sample of 12 adolescents;
5. Via structured interview, elicit feedback from adolescents, parents, and yoga instructors; use the feedback to further refine the yoga manual and other related materials.

Phase 3: Pilot RCT (Study A)

6. Conduct a pilot randomized clinical trial (n = 34) of 3 months of hatha yoga vs. group CBT for depression for adolescents aged 13-18 with major depression; we also refer to this as Study A. [Note. There will also be a Study B in which we may enroll up to an additional 20 adolescents that do not meet Phase 3 (Study A) inclusion criteria due to either low depression severity on the QIDS or recent changes in treatment. Study B will run concurrent to Phase 3/Study A. Participants will undergo the same procedures as the main Phase 3 participants. Allowing these individuals to participate will allow us to increase the size of the yoga/CBT classes, potentially making them of more value for all participants.]
7. Assess feasibility, acceptability, and safety of both the yoga intervention and comparison group;
8. Assess within-group changes on outcomes. The primary outcome will be adolescent report of depression symptom severity at 3 months, assessed by a blind evaluator. Secondary outcomes include depression severity at follow-up (9 months), and self-report of depression, functional impairment, and anxiety at 3 and 9 months.

2. BACKGROUND AND RATIONALE

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

Recent reports have shown an alarming increase in prevalence of depression in adolescents, particularly girls, as well as increased numbers of untreated depression in adolescents [1]. This is true despite improved access to health care from 2000 to 2014 across all socioeconomic groups [2] and data supporting more efficacious treatment of depression in adolescents [3]. Thus, testing alternative approaches to treating depression in adolescents, including approaches that do not rely on the limited pool of child and adolescent mental health providers, is an urgent public health priority.

2.2 Study Rationale

Yoga is an ancient Indian system of philosophy and practice [4]. In the U.S., most people who practice yoga practice *hatha* yoga, which involves training the body through breath control, physical postures, and meditation in order to promote mental and physical well-being. A meta-analysis of 12 randomized controlled trials (RCTs) of yoga for depressive symptoms in adults reported yoga was significantly better than usual care, relaxation, or aerobic exercise in decreasing depressive symptoms [5]. More recent research confirmed these findings [6, 7]. We recently conducted an RCT of adjunctive hatha yoga (vs. a health education control) for adults with current or recent major depression who were taking an antidepressant and continued to have persistent depressive symptoms (n=122) [8]. The intervention period lasted for 10 weeks, and we assessed participants for an additional 6 months. Although differences between groups in depression symptom severity were not statistically significant at 10 weeks, they were significantly different over the 6-month follow-up period, favoring the yoga arm. Thus, even in this difficult-to-treat group of adults, we found that hatha yoga had an enduring effect on depressive symptoms.

There are various plausible mechanisms by which yoga may have an impact on depression, including self-regulatory mechanisms. On the psychological level, yoga may increase self-compassion and one's ability to observe one's thoughts and feelings as subjective and transient internal experiences rather than objective and permanent reality (i.e., meta-cognitive awareness). On the biological level, yoga may lead to increased heart rate variability, reflecting an improved ability to regulate one's biological and other responses to stress.

There are fewer studies of hatha yoga in adolescents than in adults, and very few studies of the effect of yoga on mood. We were unable to find any studies that rigorously examined yoga in adolescents with clinically significant depression symptoms at baseline. Given yoga's promising results in adults, and presumed mediators, we believe that hatha yoga may be a useful and safe intervention for depression in adolescents. However, it is necessary to adapt existing hatha yoga manuals for use in depressed adolescents. Using the Participatory Action Research framework, we will adhere to step-wise guidelines for adapting manualized interventions [9] which include conducting separate focus groups with adolescents and parents; soliciting feedback from experts; making iterative revisions of an instructor manual, and conducting pilot open and randomized controlled trials. We will classify specific modifications (to be informed by focus groups and expert feedback) using the system proposed by Stirman [10] to facilitate adaptation by other research groups.

We will then conduct an open trial of hatha yoga for adolescents with depression, followed by a pilot randomized clinical trial of hatha yoga vs. group CBT for depression. We chose group CBT as this is an empirically supported treatment for depression in adolescents [11], and we plan to ultimately conduct an equivalency trial. In both trials in this project, adolescents will receive the active intervention (i.e., weekly classes) for a 12-week period. Twelve weeks was chosen because it is sufficient time for improvement in depression symptoms and to administer the comparison intervention, group CBT for depression. Adolescents will attend classes once per week as more often is likely impractical (although we will discuss this issue in focus groups). Adolescents will be asked to complete relevant homework regardless of whether they are in hatha yoga classes or CBT classes. Potential risks of both interventions include loss of privacy or breach of confidentiality, increased distress due to procedures, and ineffective intervention (i.e., lack of improvement in depression symptoms). Potential risks of yoga include mild physical injury.

3. STUDY DESIGN

In Phase 1, we will conduct focus groups with 24 adolescents with depression, with separate but concurrent focus groups for their parents (n=24). We will use focus group feedback to adapt our existing yoga program for use with adolescents. We will also separately solicit feedback from experts in depression, health, and/or yoga in adolescents. We will also create accompanying training materials and an instructor fidelity assessment scale. Enrollment period for this phase will last approximately 4 months.

In Phase 2, we will conduct an open single-arm pilot trial (n=12 adolescents) of our adapted hatha yoga to examine feasibility, acceptability, and safety, and to gather additional feedback from adolescents, parents, and yoga providers to guide further refinement of the manual. Participants will be adolescents with depression who will be in the study for 3 months; they will attend yoga classes once per week for all 3 months. Yoga instructors will also invite participants to engage in home-based yoga practice. We will also invite parents to participate in assessments regarding their child. Enrollment period for this phase will last approximately 4 months

In Phase 3, we will conduct a pilot RCT of hatha yoga vs. group CBT (study A; n=34 adolescents) to assess feasibility, acceptability, and safety of these interventions, examine preliminary outcomes of depression, functional impairment, and anxiety, as well as engagement of hypothesized mechanisms of self-compassion, and metacognitive awareness. Randomization will be blocked and stratified by gender. Participants will be adolescents with depression who will receive their assigned intervention for 3 months and then also have follow-up assessments for 3 or 6 months. We will also invite parents to participate in assessments regarding their child. A blind evaluator will assess outcomes that do not directly reference which study arm participants are enrolled in. Enrollment period for this phase will last approximately 6 or 9 months. All study procedures will occur at Butler Hospital.

Study B, which will run concurrent to Phase 3, will be for participants (n = 20 adolescents maximum) who did not meet the depression inclusion criteria or had recent changes in therapy or medications that make them ineligible for Phase 3. Enrollment will be blocked and stratified by gender (and be separate from randomization for Study A). Participants will be randomized to Phase 3 groups of hatha yoga or group CBT for 3 months, and then have follow-up assessments for 3 or 6 months. We will also invite parents to participate in assessments regarding their child.

All parts of the study will be conducted at Butler Hospital, with community participants.

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

Participants must meet all of the relevant inclusion criteria to participate in the study.

Phase 1 (Focus Group) Inclusion Criteria – Adolescents

These are designed to be similar to inclusion criteria for Phase 2 and 3, but because adolescents will not be participating in the yoga intervention and are only attending a single focus group, criteria is more inclusive than Phase 2 and 3 to reduce assessment burden.

a) Adolescents must have elevated depressive symptoms, defined by a score of 8 or higher on the PHQ-8, and a "1"or greater on at least one of the following two items: sad mood, or

anhedonia.

b) Adolescents must be aged 13-18.
c) Adolescents must be medically cleared for moderate physical activity by their primary care physician. This criterion will be assessed by adolescent or parents self-report that the adolescent has a current (dated in the past year) statement from their pediatrician that the adolescent may participate in school or camp programs including physical education.
d) Adolescents must be able to read and write English sufficient to complete informed consent and engage in interventions.
e) Adolescents aged 13-17 must assent to be in the study, and their parent/legal guardian must consent to their participation. Adolescents aged 18 must consent to be in the study.
f) Able to attend a focus group.

Phase 2, Phase 3 Study A, and Phase 3 Study B Inclusion Criteria – Adolescents

Please note, inclusion criteria for Phase 2, Phase 3 Study A, and Phase 3 Study B are identical, with the exception that, for Phase 3/Study B, we will not require elevated depressive symptoms (a) or stable treatment (b).

a) Adolescents must have elevated depressive symptoms, defined by a score of 10 or higher on the Quick Inventory of Depression –Adolescent Version-- Clinician Rating (QIDS-A-CR; [12-14]), including endorsement of either sad mood or anhedonia on the QIDS.
b) Other treatment for depression must be stable at baseline. Adolescents do not have to be in other treatment for depression, but, if they are, it must be stable with no substantive changes for the past 8 weeks. If unexpected changes in treatment occur during the study protocol period, participants can remain in the study and this treatment change will be captured as data.
c) Adolescents must be aged 13-18.
d) Adolescents must be medically cleared for moderate physical activity by their primary care physician. This criterion may be met by a current (dated in the past year) statement from their pediatrician that the adolescent may participate in school or camp programs including physical education.
e) Adolescents must be able to read and write English sufficient to complete informed consent and engage in interventions.
f) Adolescents aged 13-17 must assent to be in the study, and their parent/legal guardian must consent to their participation. Adolescents aged 18 must consent to be in the study.
g) Able to attend one of the class times.
h) Access to a private space in their home for study classes, and a device that will support use of the video platform we are using to conduct assessments and classes.

Parent Inclusion Criteria for all Phases

a) Parent/legal guardian of an adolescent who is eligible for the study.
b) Provides informed consent.
c) Able to read and write English sufficient to complete informed consent and study questionnaires.

4.2 Exclusion Criteria

Phase 1 (Focus Group) Exclusion Criteria – Adolescents

a) Adolescents may not have current suicide ideation or behavior that warrants immediate treatment. They may have passive ideation (i.e., thoughts that life is not worth living), but

may not have active suicide ideation, intent, plan, or an attempt within the previous 6 months. We will not actively assess this for Phase 1, but we will exclude an adolescent if they indicate they have active suicide ideation.

b) Adolescents cannot currently be engaged in yoga classes, as these are the study interventions.

Phase 2, Phase 3 Study A, and Phase 3 Study B Exclusion Criteria – Adolescents

Exclusion criteria for Phase 2, Phase 3 Study A, and Phase 3 Study B are identical.

a) QIDS- A-SR may not be higher than a score of 21. This ensures that adolescents are not severely depressed.
b) Adolescents may not meet criteria for the following:
    i. Autism spectrum disorder (AS) "cannot be ruled out" (via MINI), and symptoms are of sufficient severity to interfere with study treatment per clinician judgment;
    ii. Current psychotic disorder
    iii. Lifetime history of a manic episode
    iv. Anorexia or Bulimia in past 3 months
    v. Substance use disorders in past 12 months, and symptoms are of sufficient severity to interfere with study treatment per clinician judgment

    These will be assessed with the Mini-International Neuropsychiatric Interview (MINI).
c) Adolescents may not have current untreated active suicide ideation or behavior. They may not have had a suicide attempt in the previous 6 months. They may not have suicide ideation that is so severe that the study clinician judges it will interfere with study participation (e.g., if the clinician judges they need a higher level of treatment now or potentially very soon). This means that adolescents with active suicide ideation may be included if they are receiving stable mental health services (e.g., therapy, counseling) and suicidal ideation is known to the mental health provider. Adolescents may be included if they have passive ideation (i.e., thoughts that life is not worth living) but are not in active treatment.
d) Adolescents cannot currently be engaged in yoga classes, as this is the study intervention.
e) Adolescents cannot be pregnant as yoga should be modified for pregnancy [15].

Parent Exclusion Criteria for all Phases

None. Please see parent inclusion criteria above.

4.3 Study Enrollment Procedures

Recruitment and Screening

For all phases, participants will be recruited from the community and through outpatient primary care and specialty mental health clinics. We will recruit from the community using social media, schools, and flyers in local businesses that cater to adolescents. We may include advertisements on city buses that take teens to school. We will recruit on Facebook, Instagram, Craig's List, and other social media sites if needed. We will post study information on a study website hosted by Butler Hospital; social media ads and posters will direct participants to the Butler website, where participants can request contact from the study staff. When an adolescent (or parent) calls or indicates interest, a research assistant will describe the study to the adolescent and parent by telephone. If they are both interested in having the adolescent participate, the RA will assess some inclusion criteria by phone (i.e, a phone screen).

For Phase 1, the RA will assess all inclusion criteria by phone once they have verbal agreement from the adolescent and the parent. RAs will tell the adolescent and parent what types of questions will be asked as part of the screening process, and then document that both the adolescent and parent have agreed to being screened by phone prior to beginning the actual screening process. The phone screen will be used to determine eligibility; there will be no other eligibility determination. The RA will administer the PHQ-8, will inquire about age, engagement in yoga, ability to attend a focus group, and medical clearance. If the adolescent is eligible, the RA will schedule the adolescent and parent to attend focus groups that will occur within the next 30 days.

For Phase 2, Phase 3 Study A, and Phase 3 Study B, the RA will describe study procedures to the adolescent, including what questions will be asked as part of the screening process on the phone. The adolescent will be made aware that the written consent of the adolescent's parent is needed to proceed in the study itself, if the adolescent is 17 years old or younger. RAs will seek verbal agreement from the adolescent and document that agreement occurred prior to beginning the actual screening process. RAs will then assess the following inclusion criteria by phone after obtaining verbal agreement from the adolescent:

a) Adolescents must be able to read and write English sufficient to complete informed consent and engage in interventions.
b) Adolescents must be aged 13-18.
c) Able to attend one of the class times.
d) Adolescents cannot currently be engaged in yoga classes.
e) Other depression treatment is stable
f) Access to a private space in their home for study classes, and a device that will support use of the video platform we are using to conduct assessments and classes.

In addition, by phone, the RA will verify that:

a) The adolescent is currently experiencing some degree of depression symptoms (i.e., PHQ-8 >=8).
b) They are able to participate in physical activity, and either have a form signed by their pediatrician or are able to get one.

If adolescents appear potentially eligible by phone, the RA will:

a) Conduct a verbal consent (with parent if teen is 17 or younger) to send an email link and conduct a Zoom video meeting;
b) Schedule that meeting to obtain informed consent by parent (if aged 17 or younger) and assent from adolescent, or informed consent from 18 year old participant.
c) Email links to the Zoom meeting, electronic informed consent, and electronic assent for teen

Informed Consent Procedures

Research assistants will perform this process. An electronic-signed consent form will be obtained from each participant using procedures outlined by the Butler Hospital IRB. Via video call and review of an electronic version of consent/ assent forms, all participants and parents will be fully informed of the purposes and procedures of the study. On the consent form and orally, participants will be given information about: who is sponsoring the study; a description of study procedures, including the process of randomization and the nature of the assessments; risks and inconveniences; benefits; compensation for study participation; alternative treatment options;

confidentiality, including the limits to confidentiality; the voluntary nature of their participation; and who to contact should they have questions. After making sure that the participant and parent have a full understanding of the nature and purposes of the study, the research assistant will obtain assent (consent if 18) from the adolescent and informed consent from the parent. For adolescents aged 17 and under, the parent will e-sign two consent forms: one for the adolescent to participate (required), and one for the parent to participate in assessments themselves (not required for the adolescent to participate). Adolescents aged 18 may also chose to have their parents participate by completing assessments, but it is not required. Assent/consent will be documented through the individual's e-signature on the respective forms, which will be kept in the CNE instance of REDCap. Participants and parents will be invited to print a copy of the assent/consent form to keep.

In Phase 1, we will begin the focus group immediately after conducting informed consent.

In Phase 2 and Phase 3, at the BL video-based visit, we will confirm inclusion criteria previously assessed via phone screen and assess the remainder of the inclusion criteria. Parents or adolescents aged 18 will next be asked to sign a release of information form that will allow us to contact their pediatrician by fax, describe the study, and request medical clearance to participate in mild-moderate physical activity. As an alternative, we will accept a form from their pediatrician in the prior year that states the adolescent may participate in school or camp programs including physical education. If the adolescent has a mental health provider, we will ask for a release of information to contact their MH provider to provide information about the study. Doing so establishes a relationship should we need to contact them in the future due to significant clinical deterioration or the development of active suicide ideation. Adolescents cannot begin classes until we gain medical clearance.

Enrollment and Randomization

In Phase 1, participants are considered enrolled immediately after signing the consent form.

In Phase 2, once we have medical clearance to participate in physical activity from a participant, and talk with the participant to confirm their interest, they are considered "enrolled." Enrollment may occur at the BL visit or at a separate BL2 phone call (if there is a need to request and wait for medical clearance). BL2 must occur within 14 days of BL1.

In Phase 2, adolescents are invited to attend classes within a week after enrollment.

Randomization occurs in Phase 3 only. Randomization will occur at a BL2 phone call. Participants are considered enrolled at BL2 after randomization. Adolescents invited to begin the study intervention within a week after enrollment.

Documentation of Reasons for Ineligibility

All participants who express interest in the study (i.e., make contact with us regarding the study) will be tracked in a separate database along with the status of their participation. Any participant who is screened by phone for any aspect of the study including Phase 2, Phase 3 Study A, and Phase 3 Study B (even if only one inclusion criterion is assessed before the participant is determined not eligible) will have a study record documenting which inclusion criteria were assessed and the outcome of that assessment (i.e., as part of a study log). The study record is linked to the participant's name and other personal identifiers only by the study ID number. Once study

status is determined (i.e., determination that a person is not eligible and the reason), we will not retain the names of potential participants if they have not signed a consent form.

5. STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

Yoga classes are administered to a group of participants. Participants attend classes once per week; they will also be asked to practice yoga at home. Classes will take place in a room on the Butler Hospital campus; they are planned to be 45 minutes long. Registered yoga teachers will deliver the intervention. Potential risks include loss of privacy or breach of confidentiality, increased distress due to procedures, ineffective intervention (i.e., lack of improvement in depression symptoms), and mild physical injury.

Group CBT is administered to a group of participants. Participants attend groups once per week; they will also be given homework assignments. Classes will take place in a room on the Butler Hospital campus. Therapists will have a master's degree or Ph.D. in psychology or a related field (e.g., social work). Potential risks include loss of privacy or breach of confidentiality, increased distress due to procedures, and ineffective intervention (i.e., lack of improvement in depression symptoms).

COVID Modifications

In the event we are unable to hold in-person classes (i.e., due to a major public health emergency), we will hold classes via videoconference. This would be through the use of HIPAA-compliant videoconference service.

We will send information about accessing the videoconference to participants via email, according to preferences for method of contact indicated by participants/ parents/guardians during the baseline consent process.

For participants who began study prior to COVID modifications (and therefore had an opportunity to switch to remote participation after consenting to and participating in in-person participation): Prior to sending out video links and holding video-based classes, we will conduct telephone consent / assent for remote participation with parents and teens, and document that they understand risks and benefits of remote participation, and consent/ assent to participate. We will use an IRB-approved script to do this. Any participants who have already consented to receiving REDCap links via email will also be asked if they would like to receive a REDCap link that will bring them to a written version of that oral consent script, so that they may follow along with the consent.

Participants who begin study after COVID modifications will be consented in all processes at the baseline visit. These participants will have study materials (mat and blocks for yoga, or CBT workbook) mailed or dropped off at their house. In addition, these participants will be required to have their cameras on while participating in study interventions.

5.2 Handling of Study Interventions

Yoga Intervention

Yoga classes. The manualized hatha yoga program will begin with a 30-minute initial

individual session with a yoga teacher, to introduce the participant to yoga and give them a chance to privately ask any questions or express any concerns. In this individual session, teachers will focus on how to practice yoga in a way that is physically safer, and review signs that a participant should alter or back out of a pose.

Subsequently, participants will be asked to attend one 45 minute class per week for 12 weeks. Each class will consist of: introduction of a theme; pranayama (breathing practices); standing postures (asanas); floor postures; inversions; guided savasana (relaxation); and home practice assignments. Classes will emphasize breath-linked movement and moderate physical activity. Class size will range between 1 and 12 participants.

Yoga Home Practice*.* Home practice will be essential for increasing yoga "dosage." When participants first start class, we will give them a yoga mat to take home. In each class, the yoga instructor will review specific practices and recommend that participants try those practices at home. The practices will always be ones that carry with it minimal risk of injury, and instructors will go over safe practice in class. Sample practices that may be introduced for homework include: 3-part breath, a cat-cow-child sequence, and a half sun salutation. Participants may continue in the study regardless of whether they practice at home.

Yoga Instructors. The Yoga Alliance is a professional organization which sets standards for yoga teacher training. One can be a Registered Yoga Teacher (RYT) at the 200- or 500-hour level. Experienced Registered Yoga Teachers (E-RYT) at the 500-hour level have at least 4 years of experience and 2000 hours teaching, and are qualified to train teachers and provide continuing education. We will require that all study yoga teachers be RYTs and will have previous experience working with adolescents. Teachers will also have study-specific training on research methods, working with depressed adolescents, and the yoga manual. They will meet approximately monthly for supervision. There will be at least 2 trained yoga teachers. Yoga supervisors will also review audio recordings of classes to assess instructor adherence.

Yoga instructor Manual Fidelity. All classes will be audio recorded. After training, Dr. Uebelacker and Ms. Conti will rate 10% of all classes for adherence to the yoga manual. Similar to previous research, they will use an adherence scale which consists of a) a checklist of required practices or types of practices as specified in the manual; and b) ratings (satisfactory, unsatisfactory) on core principles as detailed in the manual. If an instructor leads a class that fall below 80% adherence on either scale, it may be grounds for re-training. However, because this is a treatment development study, this may also be an indicator that the manual itself needs to be clarified. Dr. Uebelacker will consult with lead yoga instructor Ms. Conti on this possibility, and make small clarifications to the manual as needed. Any larger changes deemed necessary would occur after the open trial or pilot RCT (unless they are immediately necessary for participant safety).

Group CBT

Groups. We will adapt the Stress and Your Mood manual and workbook to guide group CBT for depression [16]. This manual focuses on core CBT skills, including behavioral activation, communication and social skills, problem-solving, and cognitive restructuring. They will be given optional assignments to complete at home. Prior to the start of class, participants will have a 30-minute individual meeting with one of the group therapists to orient them to the group. Class size will range between 1 and 12 participants. There will be at least 2 trained therapists for this group.

Homework. Participants will be given optional assignments to complete at home.

Therapists. Therapists will have a master's degree or Ph.D. in psychology or a related field (e.g., social work), and will have previous experience with CBT and with adolescents. The therapist will have study specific-training and will meet approximately monthly for supervision. Dr. Uebelacker will review audio recordings to assess therapist adherence to the study manual.

CBT Therapist Manual Fidelity. Procedures will mirror procedures used for yoga teachers. After training, Dr. Uebelacker or a qualified co-Investigator will rate 10% of all groups for adherence to the therapist manual. They will use a checklist to assess fidelity to the manual for each class, and a separate scale to assess adherence to core principles of CBT. Any classes that fall below 80% adherence will be grounds for re-training.

5.3 Concomitant Interventions

5.3.1 Allowed Interventions

Once a participant is enrolled in the study, participants will not be excluded for any concomitant intervention. For example, if a participant begins outside yoga classes while they are in the study, we will record that information, but not require that they discontinue study interventions. If a participant changes their dose of antidepressant medication, or outside therapy, we will record that information, but not require that they discontinue study participation.

5.3.2 Required Interventions

None.

5.3.3 Prohibited Interventions

None.

5.4 Adherence Assessment

Yoga Participant Adherence. To be considered adherent, a participant must attend 8/12 classes and engage in home practice at least 2 times per week for 8/12 weeks (as assessed via self-report).

CBT Participant Adherence. Participant adherence is defined as number of groups attended; we define "satisfactory" adherence as attending 8/12 groups.

6. STUDY PROCEDURES

6.1 Schedule of Evaluations

Table 1. Schedule of Evaluations, Phase 1.

Assessment	Phone Screening: (Day-30 to Day-1)	Baseline, Enrollment, Visit 1 (Day 0)
Inclusion/Exclusion	**X**	
PHQ-8	**X**	
Informed Consent Form		**X**
Demographics and Psychotherapy Practice Scale-Patient Depression Care Version		**X**
Payment – Adolescent		**$35**
Payment – Parent		**$35**

Table 2, Schedule of Evaluations, Phase 2 and Phase 3.

Assessment	Type of Assessment	Phone Screening: (Up to 30 days before BL1)	Baseline 1, Visit 1	Baseline 2; must occur with 14 days of BL1	After initial class	Weekly M1, M2, M3	M1 visit	M2 visit	M3 visit	M6 visit (Phase 3 only)	M9 visit (Phase 3 only)**
Inclusion/Exclusion (A)	Interview, pre-randomize.	X	X								
Informed Consent Form (A/P)	Pre-randomize.		X								
Enrollment – Phase 2	Interview, non-blind RA		X	X							
Enrollment and Randomization – Phase 3	Interview, non-blind RA			X							
CEQ (A)	Self-report, non-blind DB				X						
CSQ-8 (A/P)	Self-report, non-blind DB								X		
Qualitative Interview (A/P)	Interview, non-blind RA								X		
Homework Questionnaire (A)	Self-report, non-blind DB					X				X	X
Injuries due to yoga (A)	Self-report, non-blind DB					X					
SAFTEE (A/P)	Interview, non-blind RA								X		
Pregnancy (A)	Interview, non-blind RA		X				X	X	X		
Other Adverse Events	Interview, non-blind RA		X	X		X	X	X	X	X	X
QIDS-A-CR (A/P)	Interview, blind RA		X				X	X	X	X	X
BDI (A/P)	Self-report, blind DB		X						X	X	X
CIS (A/P)	Self-report, blind DB		X						X	X	X

Assessment	Type of Assessment	Phone Screening: (Up to 30 days before BL1)	Baseline 1, Visit 1	Baseline 2; must occur with 14 days of BL1	After initial class	Weekly M1, M2, M3	M1 visit	M2 visit	M3 visit	M6 visit (Phase 3 only)	M9 visit (Phase 3 only)**
SCARED (A/P)	Self-report, blind DB		**X**						**X**	**X**	**X**
TMS (A)	Self-report, blind DB		**X**						**X**		
SCS (A)	Self-report, blind DB		**X**						**X**		
Yoga Practice (IPAQ format) (A)	Interview, non-blind RA		**X**				**X**	**X**	**X**	**X**	**X**
TRAQ (A/P)	Interview, blind RA		**X**						**X**	**X**	**X**
CASA (A/P)	Interview, blind RA		**X**						**X**	**X**	**X**
Psychotherapy Practice Scale – Pt Depression Care Version (A)	Self-report, blind DB		**X**								
PROMIS Sleep disturbance scale (A)	Self-report, blind DB		**X**						**X**		
Demographics (A/P)	Self-report, blind DB		**X**								
MINI (A/P)	Interview, pre-randomiz.		**X**								
MINI Mania/hypomania and Suicidality Modules (A)	Interview, blind RA								**X**	**X**	**X**
PHQ-8 (A)	Interview, pre-randomiz.	**X**									
Teen treatment arm preference (A)	Self-report, blind DB		**X**								
Perceived Cohesion Scale (A)	Self-report, blind DB				**X**				**X**		
Payment – Adolescent			**$30**				**$20**	**$20**	**$30**	**$40**	**$50**

Assessment	Type of Assessment	Phone Screening: (Up to 30 days before BL1)	Baseline 1, Visit 1	Baseline 2; must occur with 14 days of BL1	After initial class	Weekly M1, M2, M3	M1 visit	M2 visit	M3 visit	M6 visit (Phase 3 only)	M9 visit (Phase 3 only)**
Payment – Parent			**$30**				**$20**	**$20**	**$30**	**$40**	**$50**

Abbreviations: time points: M1, M2, M3 = months 1, 2, and 3, respectively; M6*, M9* = follow-up assessments at months 6 and 9, RCT only.
Assessee: A = adolescent; P = parent; A/P = both. RA = research assistant; DB = database.

** M9 visit only included for participants who signed a consent form version dated 12/1/2020 or earlier.

6.2 Description of Evaluations

Assessments will be administered by research assistants (RAs) trained in procedures to ensure confidentiality and proper management of research data. Adolescents and parents will be assessed separately; discrepancies in interview-based measures (e.g., MINI) will be resolved via consultation with Dr. Uebelacker or Yen or a qualified co-I prior to the final eligibility determination.

6.2.1 Phone Screen

Consenting Procedure

All phases will have a) agreement from adolescent to conduct screening by phone and b) informed consent from adolescent and parent/legal guardian (if adolescent is 17 years old or younger) at the first in-person visit.

For information about agreement to screening, please see section 4.3 Study Enrollment Procedures.

Screening

For Phase 1, the telephone screen must be conducted within 30 days prior to the scheduled focus group.

For Phases 2 and 3, because all inclusion criteria are verified or re-verified at BL1 (with the possible exception of medical clearance); the telephone screen may be conducted as many as 30 days prior to BL1.

Please see section 4.3 for information about what will be assessed on the telephone screen.

6.2.2a Baseline – Phase 1 (Focus groups)

Consenting Procedure – Phase 1

Written informed consent will be obtained at the baseline visit.

Please see section 4.3 for more information about the consent (and assent) procedures.

Dr. Caviness (or Dr. Uebelacker, in her absence) will inspect BL documents (consent forms, release of information) for completeness within a week after they are signed. Documents will be stored in a locked file cabinet.

Screening and Enrollment – Phase 1

In Phase 1, there is no further screening at the Baseline visit. Participants are considered enrolled once they sign the informed consent form.

Assessments – Phase 1

We will conduct focus groups with adolescents, composed of approximately 6 adolescents each, although the size will vary depending on scheduling. It is possible that some "focus groups" will consist of only one adolescent or one parent, due to scheduling or other reasons; questions for this 1:1 interview will be the same as focus group questions. We will invite parents to attend a focus group that occurs at the same time as the adolescent group. After participants sign informed consent/assent, we will collect demographic information and Psychotherapy Practice Scale-Patient Depression Care Version via a self-report questionnaire. We will then present information about yoga classes and general study design. We will ask participants for feedback on each of these aspects of the study, with a particular focus on tailoring that may be needed to increase feasibility, acceptability, safety, and efficacy for treating depression in this population. Each focus group will be no longer than 2 hours, including the consent process at the

beginning. All groups will be audio recorded and transcribed. Transcriptions will not include names or other personal identifiers. Both adolescents and parents will be paid $35 for their participation.

6.2.2b Baseline 1 (B1) – Phases 2 and 3

Consenting Procedure – Phases 2 and 3

Written informed consent will be obtained at the first baseline visit via e-signature (BL1).

Please see section 4.3 for more information about the consent (and assent) procedures.

Dr. Caviness (or Dr. Uebelacker, in her absence) will inspect BL documents (consent forms, release of information) for completeness within a week after they are signed. Documents will be stored on REDCap.

Screening – Phases 2 and 3

After informed consent/assent is complete, RAs will administer the following to ascertain inclusion criteria during BL1:

- QIDS-A-CR – Adolescent (depression symptom severity, suicide ideation)
- MINI– Adolescent and Parent (psychiatric disorders)
- TRAQ – Adolescent and Parent (depression treatment)
- CASA – Adolescent and Parent (depression treatment)
- Question pertaining to pregnancy – Adolescent (possibility of pregnancy)

RAs will also ask for proof of medical clearance for physical activity. As an alternative, we will accept a form from their pediatrician in the prior year that states the adolescent may participate in school or camp programs including physical education. If participants meet all eligibility criteria and are able to provide medical clearance for physical activity at their BL1 visit, we will then conduct the remainder of the BL1 assessments.

For participants who meet all other eligibility criteria, but for whom we need to request medical clearance to participate in physical activity from their physician, we will also conduct the remainder of the BL1. (We will then request medical clearance from their physician immediately following this visit).

For participants who do not meet eligibility criteria, we will inform adolescent and parent without stating specific reason for exclusion, to protect the confidentiality of the adolescent. We will provide referrals to the community upon request.

Baseline Assessments – Phases 2 and 3

Remaining Baseline1 assessments include:

- BDI
- CIS
- SCARED
- TMS
- SCS
- Promis – Sleep
- Yoga Practice (IPAQ format)
- Demographics
- Psychotherapy Practice Scale
- Teen treatment arm preference

Enrollment – Phase 2

If participants meet all eligibility criteria and are able to provide proof of medical clearance for physical activity at their BL1 visit, they are considered enrolled at their BL1 visit. BL1 visit date is recorded as the enrollment date. Participants for whom we need to request medical clearance for physical activity will need to have a second Baseline 2 contact (phone call) scheduled once we have obtained the medical clearance. BL2 must occur within 14 days of BL1. They are considered enrolled at BL2.

Enrollment and Randomization – Phase 3

Randomization occurs in Phase 3 only. Allowable window between BL1 and randomization (BL2 timepoint) is 14 days. Participants are considered enrolled at BL2 after randomization. The participant is invited to begin the study intervention within 1 week of randomization.

Payment – Phases 2 and 3

Payment to adolescents for completion of this visit is $30. Payment to parents for completion of this visit is $30.

6.2.3 Blinding – Phase 3

Blinding will occur in Phase 3 only. We propose to have one blinded PI and one blinded RA on this project. Dr. Uebelacker will be the non-blind PI and will primarily be responsible for supervision of the interventionists and ensuring therapist/yoga instructor adherence. Dr. Yen will be the blind PI and will be primarily responsible for the supervision of the assessors (including rating ambiguous data on outcome measures), and monitoring retention of study participants in aggregate, not by study arm. Dr. Brick, the study statistician, will be blind to group assignment (and will have no contact with participants.) When there is a question about whether a participant meets inclusion criteria, Dr. Yen will make a decision about inclusion. Dr. Uebelacker and non-blind RA will meet separately to discuss intervention-specific concerns (e.g., need to cancel class due to lack of participants). Co-I Dr. Wolff will also assist with supervising assessors, and will be blind to treatment group. Project Manager Dr. Caviness will not be blind.

To ensure that blindness will be maintained, we will have two separate REDCap modules/databases. One will contain study participant data that does not indicate participant randomized assignment; the other will have intervention-specific data (e.g., dates of sessions attended, yoga homework) that only the non-blind PI and RA will have access to.

In this study, we conduct assessments with both the adolescent and parent, typically at the same time. Both RAs are blind to treatment group at baseline, as it has not yet been assigned. The non-blind RA will conduct the randomization. For follow-up assessments, we have detailed in Table 2 above whether the blind or non-blind RA will conduct a particular assessment.

In reporting adverse events to the Independent Monitoring Committee, determination of "causal relationship" will be made by the non-blind PI only, as it may require knowledge of which intervention arm the participant is in. The standard Adverse Events Reporting Form of our IRB does not ask for intervention arm; thus risk of un-blinding from AE reporting is minimal.

Either PI can conduct suicide or other risk assessments. If the blind PI is conducting a risk assessment, she will remind the participant not to reveal the intervention arm. In the unlikely event that a risk assessment is needed during class and the blind PI needs to conduct the risk assessment, the non-blind RA will bring the participant to a neutral location for assessment.

The non-blind PI will meet with yoga instructors and CBT therapists for supervision. The

instructor/ therapist adherence ratings will be conducted by the non-blind PI and RA.

We will keep a record of any instances of un-blinding. This record will be used to improve procedures for a larger clinical trial. After all data are collected and the database is locked, the blind PI may be un-blinded so as to contribute to data interpretation.

Participants and parents cannot be blind to study intervention. However, we will present both interventions (CBT or yoga) with equipoise to all participants in written materials and orally.

6.2.4 Follow-up Visits – Phases 2 and 3

For the purposes of targeting dates for an assessment, we will consider each month = 28 days (4 weeks exactly). For all follow-up assessments, research staff will make every effort to conduct the assessment within one week before or one week after the exact due date of the assessment. However, because all data can be analyzed with modern statistical methods regardless of whether it was collected inside that window, RAs will still collect data if possible even if it is later than that two-week window. We will record optimum date for the assessment (e.g., Enrollment + 84 days for M3 assessment) as well as the actual date of the assessment.

If it is not possible to conduct study follow-up assessments in person, they will be conducted by telephone and via REDCap survey (For self-report questionnaires).

Participants will have the option of being paid in one of three ways for assessments conducted by phone:

a. We can hold the cash for them until a date when study staff may meet them in person to give them the cash.
b. If participants have signed consent to allow emails, we can send them an electronic Amazon gift card
c. We can send participants a check by mail.

Phase 2 and 3 Visits:

- Weekly for 12 weeks
  - Study classes/groups
  - Homework Questionnaire
  - Injuries due to yoga
  - CEQ;
  - Perceived Cohesion Scale (after initial class only)
  - Any other AEs reported to RAs

- Month 1
  - Pregnancy question
  - Any other AEs reported to RAs
  - QIDS
  - Yoga Practice (IPAQ format)
  - Payment: adolescent - $20; parent - $20

- Month 2
  - Pregnancy question
  - Any other AEs reported to RAs
  - QIDS
  - Yoga Practice (IPAQ format)
  - Payment: adolescent - $20; parent - $20

- Month 3 (Final evaluation for Phase 2)
    - CSQ-8
    - Qualitative interview
    - SAFTEE
    - Pregnancy question
    - Any other AEs reported to RAs
    - MINI – Mania/hypomania module and Suicidality module
    - QIDS
    - BDI
    - CIS
    - SCARED
    - TMS
    - SCS
    - PROMIS-Sleep
    - Yoga Practice (IPAQ format)
    - TRAQ
    - CASA
    - Perceived Cohesion Scale
    - Payment: adolescent - $30; parent - $30

Phase 3 Visits Only:

- Month 6
    - Homework questionnaire
    - Any other AEs reported to RAs
    - QIDS
    - BDI
    - CIS
    - SCARED
    - Yoga Practice (IPAQ format)
    - TRAQ
    - MINI – Mania/hypomania module and Suicidality module
    - CASA
    - Payment: adolescent - $40; parent - $40
    -
- Month 9 (Final evaluation for Phase 3)
    - Homework questionnaire
    - Any other AEs reported to RAs
    - QIDS
    - BDI
    - CIS
    - SCARED
    - Yoga Practice (IPAQ format)
    - TRAQ
    - MINI – Mania/hypomania module and Suicidality module
    - CASA
    - Payment: adolescent - $50; parent - $50

NOTE: M9 visit only included for participants who signed a consent form version dated 12/1/2020 or earlier.

6.2.5 Completion/Final Evaluation – Phases 2 and 3

Even if adolescents drop out of study treatment, we will attempt to collect data at all assessment

points if adolescents and parents agree to it.

7. SAFETY ASSESSMENTS

For yoga, the only expected adverse event is:

- Physical injury (mild). This includes mild aches or pain during or shortly after yoga classes.

For group CBT, there are no expected adverse events.

Risks of study participation include:

- Coercion
- Increased distress due to intervention or assessment procedures
- Ineffective intervention.
- Loss of privacy or breach of confidentiality

Risks and measures to reduce those risks are detailed below.

Potential coercion. It is possible that individuals (adolescents, parents) may feel coerced into participating. This risk is a serious one but we believe that it is highly unlikely given informed consent processes and the ease with which one may withdraw from the study. We will follow standard procedures for obtaining informed consent. Study staff will fully explain the study procedures, risks, benefits, and alternatives to all potential participants and their parents. Parents and adolescents will be aware that they may refuse to participate or drop out of the study at any time without any negative repercussions from study staff, health care providers, or affiliated institutions.

Confidentiality and loss of privacy. Study personnel will be collecting considerable information about the study participants. This may create some distress and could cause social and psychological risk if released inappropriately. This risk is a serious one but we believe that it is highly unlikely.

All information will be collected and handled by research staff trained to deal appropriately with sensitive clinical issues. All information will be treated as confidential material and will be available only to research and clinical staff. All data collected will be entered into an electronic database which is stored on a secure server (REDCap) that is backed up on a daily basis. Patient identifying information will be stored in a separate database and will be password protected and stored on a secure server. All paper files will be kept in a locked filing cabinet. Audio recordings will be stored on a secure server or kept in a locked filing cabinet. No subject will be identified in any report of the project.

REDCap is a secure, web-based application developed by Vanderbilt University for building and managing surveys and databases. It is primarily designed to support online or offline data capture for research studies, quality improvement, and operations. REDCap provides easy data manipulation (with audit trails for reporting, monitoring and querying patient records), real-time data entry validation, and an automated export mechanism to common statistical packages.

Care New England's instance of REDCap is hosted within the Care New England data center in Warwick, RI. This REDCap instance is role-based and is fully integrated with CNE's Active Directory structure. It enjoys 24/7/365 enterprise-level support and security inherit to CNE's HIPAA-compliant data center. Network transmissions (data entry, survey submission, and web browsing) to and from

REDCap are protected via TLS 1.2 encryption. REDCap's data is stored on encrypted servers within CNE's data center.

The REDCap Consortium is composed of thousands of active institutional partners in over one hundred countries who utilize and support REDCap. REDCap was developed specifically around HIPAA-Security guidelines, and more information about the consortium and system security can be found at http://www.projectredcap.org/.

Due to the nature of text messaging technology, there is a small, but potential, privacy risk when communicating through text messages. Text message communications are not encrypted and therefore this information can be read if intercepted while in transit. Although we have a strict patient confidentiality policy there is a possibility for the text messaging communications to be intercepted or accessed without the participant's authorization. This will be made clear in the informed consent process, and we will remind participants not to send sensitive information by text. It is important to note that we will only be conveying general information by text messaging. No confidential or sensitive information will be sent by text message at any time. Text messages will contain information about scheduling only. Text messages will be sent from a dedicated password-protected study cell phone. The loss of privacy is a serious risk but we believe that it is highly unlikely as we have extensive experience taking measures appropriate to safeguarding confidential information. Participants may be included in the study even if they decline to have text messages sent to them.

We will ask parents/participants to sign a release of information so that we may communicate with their primary care provider and their specialty mental health providers (if any) about a) medical clearance for mild/ moderate physical activity; b) any serious mental health concerns that may arise. Although this could present a risk to confidentiality, we believe this is outweighed by concerns about the patient's safety.

Finally, being part of a focus group or a group intervention carries with it a risk of loss of privacy. We will remind participants of this risk in the informed consent process, and also ask them to keep information learned about other group members, including the fact they were in the group, private. This risk may be slightly increased when classes are conducted via videoconference. To decrease this risk, we will ask that all participants view video classes in a private location in their home; we will also make sure participants understand that we cannot guarantee all participants will do this.

Increased distress due to assessment or intervention procedures. It is possible that some adolescents will experience increased intrapersonal or interpersonal psychological distress as a result of participating in assessments or intervention. In the vast majority of cases, we believe that any increased distress experienced will be mild and transitory in nature. The risks of possible distress due to the assessment and treatment procedures will be minimized by: a) using assessments and procedures which have been widely used in previous research studies; b) allowing participants to refuse to answer any question or withdraw from the study at any time; c) training yoga instructors in how to minimize and manage distress that may occur in class; and d) having study MPIs Drs. Yen (a licensed clinical psychologist with expertise in adolescent suicidality), Uebelacker (a licensed clinical psychologist), and co-I Dr. Wolff (a licensed clinical psychologist with expertise in adolescent suicidality), or their designee (who will be a licensed health professional) in their absence, on call to counsel participants should they report experiencing distress.

Physical injury. Because yoga is a physical activity, there is a small risk of physical injury for those participants who are in study yoga classes. The risk of physical injury will be minimized by: a) requiring all participants in yoga classes to be cleared by their primary care provider for moderate physical activity; and b) requiring all instructors to be registered yoga teachers with experience in directing people in how to achieve yoga postures without physical injury. Class content will be designed

to accommodate the needs of yoga-naïve students who are not currently physically active. By presenting modifications of all postures, and by using props (e.g., folding chairs, blocks, straps, and blankets), the risk for injury will be minimized. Injuries due to yoga will be monitored at frequent intervals during this part of the study.

To minimize risk of physical injury for yoga classes conducted via videoconference, we will do all of the above. In addition, we will only use poses that have been successfully used in in-person classes. Of note, we have had 19 participants enroll in yoga classes as of 3/13/2020, with no adverse events of any severity level related to participation in yoga class. Therefore, we believe that conducting yoga via videoconference does not result in any increased risk to teens. The initial 1:1 session with a newly enrolled participant and the yoga teacher will also include a discussion of ways to decrease risk of injury.

Ineffective intervention. It is possible that some participants will not experience improvements in depression symptoms. The risk of possible ineffective intervention will be minimized by the fact that study participants will continue with their current medication or other treatment for depression. Study participants may choose to discontinue study participation at any time.

Given that all participants will have risk factors for suicidality (i.e., depression), some participants may experience suicide ideation or behavior in the course of study participation. Significant risk for suicide will be defined by QIDS item 12 score of 1 or greater (indicating suicide ideation or intent or behavior) OR the report of a desire or intent to hurt oneself to study staff. Whenever staff members identify an individual with significant risk for suicidality, we will use a standard protocol for managing this problem. Study staff will contact either Dr. Uebelacker, Yen, or Wolff. They will be available during regular business hours, and have extensive experience managing this issue. After hours, there is always a licensed mental health clinician available on call by cell phone.

When a clinician is asked to conduct an immediate evaluation, they will conduct a suicide risk assessment. The clinician will determine whether it is necessary to take immediate action to prevent the participant from causing harm to themselves. If needed, the study clinician may ask to speak to a parent and/or have a family member or ambulance bring the person to Butler Hospital or another hospital. If the participant is not in immediate danger of hurting themselves, we will take the following actions. First, we will work to develop a safety plan with the patient and encourage them to discuss this with their parents and/or treatment providers. Second, we will inform the parent(s) (for participants aged 13-17) to ensure that they are aware of the seriousness of the participant's symptoms and their suicidal ideation. If participants are 18, we will ask for permission to talk with a family member. Families will receive detailed psychoeducation regarding suicide risk including removing potential suicide means (e.g., guns, knives); being alert to mood changes, suicidal statements, etc.; and learning how to obtain emergency services. Finally, we will contact their primary care physician or other clinician to inform them of the suicidality. We will urge the participant/parent to make an appointment with that provider to discuss treatment options. Regardless of outcome, suicide assessments are always documented in writing.

Participants may also show significant clinical deterioration, as defined as a QIDS total score of 16 or greater and an increase in QIDS score of 6 or greater from the previous QIDS assessment. This will also trigger a clinical evaluation and a determination of the best course of action for the adolescent based on clinical judgment. Typically, this will include notification of a parent and outpatient mental health provider (if the participant has one) or offer of referrals to an outpatient provider. Actions could also include facilitation of higher levels of care (e.g., inpatient hospitalization).

A participant who has undergone a suicide risk assessment or who has had clinical deterioration may continue to participate in the study unless the study PIs, in concert with the participant's parent and healthcare providers, deem study participation to increase risk for this particular participant. Participants who are hospitalized due to concerns about suicidality may be discontinued from the study if parents/

clinicians/ MPIs determine it to be in the best interest of the participant. However, they may also continue if that is determined to be in the best interest of the participant.

Additional Protections for Vulnerable Subjects

For study participants who are minors (ages 13-17), parental consent will be required in addition to assent. We will ensure that adolescents and their parent(s) are fully informed of the purposes and procedures of the study both verbally and through a written description contained on the assent/consent forms. As an additional protection to research participants who are minors, all participants will be informed that disclosure of information regarding abuse will result in reporting the event to appropriate state authorities. Participants will also be informed that any disclosure regarding potentially life-threatening behavior – e.g., severe suicidal ideation, IV drug use – will be reported to their therapists and/or primary care provider and parents. When a report to a parent is made, we will also ensure that families will receive detailed psychoeducation regarding suicide risk including removing potential suicide means (e.g., guns, knives); being alert to mood changes, suicidal statements, etc.; and learning how to obtain emergency services. It is possible that situations will arise in which research assistants or group leaders are provided with information by adolescents or parents which they are legally and ethically obligated to disclose (e.g., suicidal or homicidal intent, harsh disciplinary practices, sexual abuse). All participants are informed in advance through the process of informed consent of the legal and ethical obligations of study staff should these issues arise. Whenever possible, study staff will handle these situations therapeutically. For example, if time limits and safety concerns allow, parents will be informed in advance that a report must be made and provided the opportunity to participate in the mandated report process. Research staff will contact the MPIs who will be responsible for any on-site clinical decision-making.

Potential Benefits

Potential benefits include: enjoyment of yoga classes or better physical health (for those taking yoga) and increased knowledge about coping skills (for those randomized to group CBT). Potential benefits of the focus groups include the opportunity to provide input on how to manage an important clinical problem.

Risk-Benefit Ratio.

We believe that most serious risks (e.g., loss of confidentiality, major psychological distress due to study participation, or serious physical injury due to yoga participation) to subjects are very unlikely. We have attempted to minimize these risks (described above). While some risks may be more likely to occur (e.g., minor, transient psychological distress), these risks are much less serious. The risk of ineffective treatment is a serious risk, but one which: 1) is minimized through safeguards described above; 2) is common to any treatment for depression. Therefore, the potential benefits of the proposed study seem to outweigh the potential risks of this study for the individual participants.

7.1 Specification of Safety Parameters

Safety issues will be minimal in Phase 1 given that participation involves only a single focus group, no yoga classes, and no formal assessment of suicidality. However, should an issue arise (e.g., a voluntary report of suicide ideation from one of the adolescent participants), staff would manage it in the same way that they would manage it in Phases 2 and 3.

Please see Table 3 for a summary of safety issues, how they are assessed, when they are assessed, and relevant staff actions.

Table 3. Assessment and Management of Safety Issues, Summary, Phases 2 and 3.

Safety Issue	How assessed	When Assessed in Phase 2/Phase 3	Relevant Research Staff Actions
Suicidality	QIDS, BDI, MINI Participant/parent report to research staff	B1, M1, M2, M3, M6*, M9* B1, M3, M6*, M9* Any point	Immediate clinical assessment as described in DSMP
Clinical deterioration	Change in QIDS score	M1, M2, M3, M6*, M9*	Immediate clinical assessment as described in DSMP
Injuries due to yoga	Structured self-report	Weekly during first 3 months	Follow until resolution; may result in changes to yoga instructor manual
Pregnancy	Single interview question	BL1 (exclusion) M1, M2	Discontinuation from intervention
Other AEs	SAFTEE CASA Participant/parent report to research staff	M3 BL1, M3, M6*, M9* Any point	If related to study participation, follow resolution; potential changes to procedures particularly if AE is also unexpected

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

See Table 3.

7.3 Adverse Events and Serious Adverse Events

Adverse Event (AE) definition: An adverse event (AE) is any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease which either occurs during the study, having been absent at baseline, or if present at baseline, appears to worsen. Adverse events are to be recording regardless of their relationship to the study intervention.

Serious Adverse Event (SAE) definition: A serious adverse event (SAE) is one that meets one or more of the following criteria:

- Results in death
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred; includes a suicide attempt or drug overdose)
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect

An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event

may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Study staff will record all reportable events with start dates occurring any time after informed consent is obtained at least until the final day of study participation. Each time participants attend yoga classes, we will inquire about injuries due to yoga. For all participants in either the open trial or pilot RCT, at Month 3 (end of intervention), study staff will administer the SAFTEE in order to inquire about the occurrence of AE/SAEs during the previous 3 months. This allows us to systematically assess number of adverse events, severity, and resulting impairment. Finally, any time a participant (or parent) reports an adverse event to any staff member, a research assistant will contact the participant or parent or both to ascertain information for recording of the adverse event. For adverse events ascertained by any of these three possible methods, the research assistant gets information on what happened, start and stop dates, severity, functional impact, interactions with healthcare professionals, perceived cause, and possible relation to study participation.

7.4 Reporting Procedures

Once staff members report an AE or SAE to MPIs, Dr. Yen or Uebelacker (and only Dr. Uebelacker in Phase 3, as she is not blind in Phase 3) will code severity, causal relationship, and whether the event was expected. If necessary, she will seek further information from the participant or parent or other source before coding.

AEs will be coded on a weekly basis. Any potential SAE will be immediately reviewed by one of the MPIs (or a qualified designee in her absence) and coded; this coding will subsequently be reviewed by the SMC (Safety Monitoring Committee). Coding of AEs and SAEs occurs on a study AE case report form.

SAEs that are unanticipated, serious, and possibly related to the study intervention will be reported to the Safety Monitoring Committee (SMC), IRB, and NCCIH in accordance with requirements. We will use the Butler Hospital IRB-approved AE report form.

- Unexpected fatal or life-threatening SAEs related to the intervention will be reported to the IRB, NCCIH Program Officer, and SMC within 3 days of the investigator becoming aware of the event. Other serious and unexpected SAEs related to the intervention will be reported within 7 days. These timeframes follow guidance from NCCIH and are consistent to local IRB policies.

Anticipated or unrelated SAEs will be handled in a less urgent manner but will be reported to the SMC, IRB, and other oversight organizations in accordance with their requirements, and will be reported to NCCIH on an annual basis.

- Unrelated SAEs that are fatal or life threatening must be reported to the Butler Hospital IRB within 7 days of the investigator becoming aware of the event.
- Unrelated SAEs that are not fatal or life-threatening must be reported to the Butler Hospital IRB annually.

All other AEs documented during the course of the trial will be reported to NCCIH on an annual basis by way of inclusion in the annual report and in the annual AE summary which will be provided to NCCIH and to the SMC. The SMC Report will state that all AEs have been reviewed.

7.5 Follow-up for Adverse Events

Any SAEs related study participation will be followed for outcome information until resolution or stabilization. Follow-up reports will be submitted to the IRB, SMC, or NCCIH as required in each specific instance.

7.6 Safety Monitoring

The NCCIH requires that all Human Subjects research studies undergo independent monitoring, and NCCIH Program Officials will provide specific guidelines to the PI for the study.

8. INTERVENTION DISCONTINUATION

Adolescents will be discontinued from an intervention in the following circumstances:

- If a parent, the adolescent, their primary care provider, or their mental health provider does not believe it is in the best interest of the adolescent to continue. As soon as an MPI is informed of this, she will speak with the participant about discontinuation. There may be circumstances (e.g., worsening depression, an injury in yoga class) when the MPI reaches out to a primary care provider, MH provider, or parent to actively inquire if they have concerns about the adolescent continuing to participate.
- If a parent or adolescent choose to discontinue the adolescent's attendance.
- If one of the MPIs, in consultation with the relevant instructor or therapist, finds the adolescent to be so disruptive to the rest of the class that they have a repeated and substantive negative impact on the other participants.
- If the adolescent does not or is unable to follow guidelines regarding being in a private space when participating in the video-based intervention.

Participants will continue with subsequent assessments with their (parent and adolescent) permission. Assessment schedule and assessments used will not change.

9. STATISTICAL CONSIDERATIONS

9.1 General Design Issues

Our primary overall objective for this pilot project is to develop procedures and manuals, and acquire supportive data on feasibility and acceptability that will prepare us to conduct a fully-powered non-inferiority design trial of hatha yoga vs. group CBT for depression in adolescents.

Because this is a treatment development study, we have chosen our sample sizes as being sufficient to assess feasibility and acceptability. This study is not powered to assess differences (or non-inferiority) between treatments.

9.1.1 Summary of Aims, Endpoints, and Data Analytic Strategy.

Table 4 summarizes each aim, the target endpoint, and the data analysis strategy, where applicable.

Table 4. Summary of Aims, Endpoints, and Analyses.

Aim/Objective	Endpoint	Analyses
Phase 1 – Focus Groups		
Conduct focus groups with adolescents and parents	Conducted up to 4 focus groups with adolescents and parents	Qualitative analysis – see description below.
Solicit feedback from experts in depression, health, and/or yoga in adolescents	Feedback received from experts in relevant areas	Qualitative analysis – see description below.
Create a manual, training materials, and fidelity assessment scale for instructors	Draft instructor manual, instructor training materials, and fidelity assessment scale created	N/A
Phase 2 – Open Trial		
Pilot the yoga intervention	12 adolescents enrolled & follow up assessments completed	N/A
Assess feasibility, acceptability, and safety of both the yoga intervention and the comparison group	See Table 5 for a complete list.	Descriptive statistics for feasibility, acceptability, and safety. See Table 5.
Via structured interview, elicit feedback from adolescents, parents, and yoga instructors	Revise draft of instructor manual, instructor training materials, and fidelity assessment scale	Qualitative analysis – see description below.
Phase 3 – Pilot RCT, Study A and B		
Pilot RCT of hatha yoga vs. group CBT for depression	34 adolescents enrolled & follow up assessments completed (plus any Study B participants)	N/A
Assess feasibility, acceptability, and safety of both the yoga intervention and the comparison group ** This is primary **	See Table 5 for a complete list (Endpoints examined separately for main participants and study B participants; also examined separately for participants consented pre-COVID and post-COVID)	Descriptive statistics (see Table 5) and qualitative data analysis
Assess within-group changes on outcomes. The primary outcome will be depression symptom severity at post-intervention (M3). Secondary outcomes include depression severity at follow-up (9 months), and self-report of depression, functional impairment, anxiety, and sleep at post-intervention (M3) and 9 months. ** This is exploratory **	Endpoint = post-intervention (M3) (Endpoints examined separately for main participants and study B participants; also examined separately for participants consented pre-COVID and post-COVID)	Within-subjects t-tests (e.g., from pre-intervention to post-intervention/M3). We will conduct analyses separately by treatment group. We will calculate effect sizes (Cohen's d) from pre- to post-treatment/M3, with corresponding confidence intervals.
Assess within-group changes on self-compassion and meta-cognitive awareness ** This is exploratory **	Endpoint = post-intervention (M3) (Endpoints examined separately for main participants and study B participants; also examined separately for participants consented pre-COVID and post-COVID)	Within-subjects t-tests (e.g., from pre-intervention to M3). We will conduct analyses separately by treatment group.

9.1.2 Description of Assessment Instruments

Acceptability and Feasibility. Intervention credibility and patient expectations for intervention

success at baseline will be measured with the Credibility Expectancy Questionnaire (CEQ) [17]; this is administered after their initial class. The Client Satisfaction Questionnaire (CSQ-8) [18] will be used post-treatment to assess satisfaction with treatment. We will also use qualitative responses to a detailed post-treatment interview to gain participants' and parents' feedback about intervention components and research procedures. Finally, it is critical that the amount of yoga practice at home be measured as accurately as possible. Participants will complete a yoga home practice questionnaire on a weekly basis. This tool was designed to capture both brief "micro" practice (e.g., focusing on breathing for a few minutes) as well as more extended home practice (e.g., engaging in a 15-minute asana routine). The tool will yield three indices of home practice: frequency of extended home practice, minutes of extended home practice, and frequency of micro home practice.

***Participant safety*.** After each home practice questionnaire (i.e., weekly during the intervention period), we will ask participants and parents whether participants experienced any injuries as a result of yoga. At the end of the study intervention (M3), we will administer the Systematic Assessment of Treatment-Emergent Events – General Inquiry (SAFTEE) [19]. This allows us to systematically assess number of adverse events, severity, and resulting impairment. To assess pregnancy, the adolescent will be asked in private whether there is a possibility of pregnancy. If they report that they may be pregnant, either at baseline or during follow-up, they will be excluded from study participation as our yoga protocol is not modified for pregnancy. Finally, any time a participant (or parent) reports an adverse event to any staff member, a research assistant will contact the participant or parent or both to ascertain information for recording of the adverse event. For adverse events ascertained by any of these three possible methods, the research assistant gets information on what happened, start and stop dates, severity, functional impact, interactions with healthcare professionals, perceived cause, and possible relation to study participation. For more information and details on coding of AEs, please see DSMP.

Note that the QIDS also serves as a safety assessment, as it allows staff to assess a) clinical deterioration and b) suicidality. The BDI also assesses suicide. Any suicidality or clinical deterioration triggers a risk assessment. An AE/SAE is recorded if the participant meets criteria for an AE/SAE (see DSMP)—i.e., makes an attempt to hurt themselves, does hurt themselves, or is hospitalized. Suicide ideation or clinical deterioration in and of themselves do not necessarily constitute an AE.

***Assessment of depression*.** In order to characterize the sample, we will assess whether participants meet criteria for major depressive disorder using relevant modules of the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID [20]). We will also use the MINI to determine whether participants meet exclusionary criteria. Our primary outcome of depression severity (adolescent interview) will be assessed using the 16-item QIDS-A-CR [12, 13] which has been psychometrically validated for adolescents [14]. The Patient Health Questionnaire – 8 item (PHQ-8;[21]; does not include a suicide item) will be used in an interview format for screening purposes only, as it is simple to administer.

Assessment of secondary outcomes. Adolescents will complete the Beck Depression Inventory-II (BDI; [22], a self-report measure of depression symptom-severity. We will also assess impairment using the Columbia Impairment Scale (CIS; [23]), which is a 13-item, self- or parent-report, that measures four areas of functioning: interpersonal relations, broad psychopathological domains, functioning in job or schoolwork, and use of leisure time. Items are rated on a Likert scale ranging from 0 (no problem) to 4 (very big problem). Anxiety will be assessed by revised version of the Screen for Child Anxiety Related Emotional Disorders (SCARED-R; [24, 25]), a 41-item self-report questionnaire designed to measure symptoms and severity of anxiety disorders in children age 8 to 17. We will assess sleep using the 8-item PROMIS Sleep Disturbance questionnaire, which has been validated in adolescents [26].

Assessment of potential mechanisms of action. We will assess metacognitive awareness (decentering) with the Toronto Mindfulness Scale (TMS), which has a decentering subscale and a

curiosity subscale [27]. We will assess self-compassion with the 26-item Self-Compassion Scale (SCS)[28]. This scale can yield a general self-compassion score and has previously been used with adolescents [29].

Other assessments. Finally, we will use the International Physical Activity Questionnaire (IPAQ) [30], a self-report measure of physical activity. We have also adapted this scale to measure amount of yoga practice participants engaged in during the follow-up time period. We will assess antidepressant medication use with the interview-based Treatment Response to Antidepressant Questionnaire (TRAQ) [31]). We will use the Child and Adolescent Services Assessment (CASA)[32] interview to assess other mental health treatment. If a participant is engaged in psychotherapy but the participant and parent are unclear as to whether it is CBT, we will use the Psychotherapy Practice Scale-Patient Depression Care Version [33] to help determine whether it is likely that the participant is engaged in CBT. This questionnaire will be modified to include some open-ended questions about the nature of the participant's psychotherapy. We will use the Perceived Cohesion scale to assess group cohesion.

9.2 Sample Size and Randomization

9.2.1. Sample Size

This project consists of three phases: In Phase 1, we will conduct focus groups with up to 24 depressed adolescents and 24 parents. This should be a large enough sample to gain sufficient feedback on ways to make yoga classes an acceptable and feasible intervention. In Phase 2, we will pilot the yoga intervention in a sample of 12 adolescents. In Phase 3, we will conduct a pilot RCT (n=34; with a possibility of 20 additional adolescents in Study B). In Phases 2 and 3, we will assess feasibility, acceptability, and safety of the interventions and research design, and examine key outcomes within relevant confidence intervals. This phase of the study is not designed to be adequately powered to assess efficacy; rather, it is focused on feasibility, acceptability, and safety. (Text also in DSMP.)

9.2.2. Treatment Assignment Procedures

Participants in Phase 3 will undergo randomization. Eligible individuals who consent to participate will be randomly assigned to yoga or group CBT. There are separate randomization tables for Phase 3/Study A participants and Study B participants. Eligibility (i.e., that the participant meets all inclusion criteria) and group (Study A/B) are determined prior to randomization. Our study statistician who has no contact with study participants and will have no access to outcome data until database lock, will create randomization tables using Microsoft Excel and upload to our data collection system (REDCap) prior to the start of recruitment for the pilot RCT. Randomization will be stratified by gender. We will use variable sized block randomization, with randomly ordered block sizes of 4, 6, or 8.

Study staff will not have access to randomization tables. When a person is deemed eligible, study staff will verify the stratification variables in REDCap and then click the "RANDOMIZE" button.

9.3 Definition of Populations

All data analysis will use the intent to treat population and use all available data. There is no per protocol analysis planned.

9.4 Interim Analyses and Stopping Rules

9.4.1. Interim analysis

There is no interim data analysis plan.

Data analysis of Phase 1 qualitative data will occur during and immediately after data collection in Phase 1.

Data analysis of Phase 2 and 3 data will occur at the end of Phase 2, midway through Phase 3, and at the end of Phase 3 (for feasibility and acceptability outcomes). (Text also in DSMP.)

9.4.2 Halting Rules

If there are any SAEs judged related to the study intervention, we will halt the study intervention until an ad hoc safety review is convened with the SMC, MPIs, and other relevant study staff. The safety review will determine whether the study should continue per protocol, proceed with enhanced monitoring, be further investigated, be discontinued, or be modified and then proceed. (Text also in DSMP.)

Subsequent review of serious, unexpected, and related AEs by the SMC, IRB, the sponsor(s), or relevant local regulatory authorities may also result in suspension of further study interventions. The study sponsor(s) retain the authority to suspend additional enrollment and study interventions /administration of study product for the entire study, as applicable. (Text also in DSMP.)

This study will be stopped prior to its completion if: (1) the intervention is associated with adverse effects that call into question the safety of the intervention; (2) difficulty in study recruitment or retention will significantly impact the ability to evaluate the study endpoints; (3) any new information becomes available during the trial that necessitates stopping the trial; or (4) other situations occur that might warrant stopping the trial. (Text also in DSMP.)

9.5 Outcomes

9.5.1 Primary Outcome

There is no single primary outcome, as this is a treatment development study.

We monitor treatment development outcomes (correspondingly described in Table 5) throughout Phases 2 and 3. Target outcomes were chosen on face validity, clinical experience, and, when available, relevant clinical literature. After the pilot open trial (Phase 2), and at 2 time points throughout the Phase 3 pilot RCT (i.e., after enrolling 17 patients and 34 patients), the scientific team will convene to discuss how our actual procedural outcomes compare to the target outcomes. Discrepancies will result in: 1) investigation (using qualitative or other data) of the reason for the failure to meet this outcome; and 2) discussion amongst the research team. Depending on the nature of the discrepancy, we may modify recruitment procedures, assessment procedures, instructions to participants, instructor training procedures, or other aspects of the trial. In addition, Drs. Uebelacker and Caviness and the lead yoga instructor will review any adverse events that are possibly, probably, or definitely related to the study intervention to determine whether any changes need to be immediately made to the yoga instructor manual to prevent such events from occurring in the future.

Primary data analyses will be focused on feasibility and acceptability (see Table 5) using intent-to-treat population. Study measures and endpoints will continue to be collected for all enrolled participants, even in the event of premature discontinuation of the study intervention. To mitigate the problem of missing data, our RAs will try to reach participants to encourage them to schedule/complete the assessment via multiple methods that a participant (and their parent) have said are acceptable, including texting, voicemail, or email.

Table 5. Target Outcomes – Phase 2 and 3.

Description (Assessment method)	Target
Feasibility and Acceptability-- Hatha yoga, CBT	
Acceptability (qualitative interview)	Most feedback positive; few substantive negative comments. Negative comments used to enhance procedures. Comments regarding video-based vs.in-person classes used to guide decisions about modality for future research.
Credibility at baseline (CEQ)	Average > 15 (i.e., midpoint score between low and high credibility) on each of 3 items
Expectancy at baseline (CEQ)	Average > 15 (i.e., midpoint score) on each of 3 items
Program satisfaction (CSQ-8)	Average > 24 (or a mean score of 3 on each of the 8 items)
Home practice (homework questionnaire)	70% of yoga participants engage in home practice at least 2 times per week for 8/12 weeks.
Class attendance	70% of all participants complete 8/12 classes.
Instructor adherence (Adherence measures)	Yoga instructors achieve at least 80% adherence on a random subset of classes taught
Safety	
Adverse events (SAFTEE; injuries due to yoga)	No serious adverse events or injuries that are possibly, probably, or definitely related to study participation. Any AEs related to study participation might lead to changes in yoga manual or other relevant study procedures, particularly if AE is unexpected.
Feasibility and Acceptability—Research Procedures	
Recruitment rate	Average of 3 enrolled per month
Retention rate	At least 90% complete M1 assessment, 85% complete M2 assessment, 80% complete post-intervention endpoint (Month 3) assessment, 75% complete M6 and M9 follow-up assessments
Completeness of self-report instruments and interviews	All self-report instruments will have at least 80% of items completed; interviews will have at least 90% of items completed

Note: we will look at outcomes for the entire group of enrolled participants for Phase 2 and Phase 3. In addition, in Phase 3, we will examine outcomes for 2 sets of subgroups:

a. Study A vs. Study B
b. Pre-COVID enrollment (including those who participated in some in-person and some video classes, which is the majority of the Pre-COVID enrolled group) vs. Post-COVID enrollment (i.e., those who consented and started video-based classes from the start).

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9.5.2 Secondary/Exploratory Outcomes

In both Phase 2 and Phase 3, exploratory outcomes include change in depression, impairment, anxiety, and potential mechanisms of action over time.

Specifically, we will look at change over time the in the following variables. The primary outcome in a subsequent efficacy study is in **bold and underlined**. Secondary outcomes are in standard text. *Potential mechanisms are in italics.*

- **Depression, Adolescent report: change in QIDS from BL to M3**; BL to M6 (phase 3 only), and BL to M9 (phase 3 only)

- Depression, Adolescent report: change in BDI from BL to M3; BL to M6 (phase 3 only), and BL to M9 (phase 3 only)
- Depression, Parent report: change in QIDS from BL to M3; BL to M6 (phase 3 only), and BL to M9 (phase 3 only)
- Depression, Parent report: change in BDI from BL to M3; BL to M6 (phase 3 only), and BL to M9 (phase 3 only)
- Functional impairment, Adolescent report: change in CIS from BL to M3; BL to M6 (phase 3 only), and BL to M9 (phase 3 only)
- Functional impairment, Parent report: change in CIS from BL to M3; BL to M6 (phase 3 only), and BL to M9 (phase 3 only)
- Anxiety, Adolescent report: change in SCARED-R from BL to M3; BL to M6 (phase 3 only), and BL to M9 (phase 3 only)
- Anxiety, Adolescent report: change in SCARED-R from BL to M3; BL to M6 (phase 3 only), and BL to M9 (phase 3 only)
- Sleep Disturbance, Adolescent report: change in PROMIS- Sleep disturbance from BL to M3

- *Mindfulness, Adolescent report: change in subscales of TMS from BL to M3; BL to M6 (phase 3 only), and BL to M9 (phase 3 only)*
- *Self-Compassion, Adolescent report: change in SCS from BL to M3; BL to M6 (phase 3 only), and BL to M9 (phase 3 only)*

9.6 Data Analyses

Qualitative Data Analysis

Focus groups (Phase 1) or interviews (Phase 2, 3) will be recorded and transcribed. We will use a template organizing style to analyze qualitative data [34]. Dr. Uebelacker will oversee the process. She will develop an initial codebook with *deductive* codes. *Inductive* codes capturing emergent themes will arise from team-level review of the transcripts. Once the codes are developed, members of the scientific team will independently code remaining transcripts; 20% of transcripts will be double coded and reviewed to ensure coding fidelity. Information gleaned will then be reviewed by the scientific team and used to modify manuals and procedures.

Quantitative Data Analysis

In Phase 2 and Phase 3, we will use descriptive statistics to summarize all variables. We will also conduct exploratory analyses of change over time in depression (which will be the primary outcome in an efficacy study), impairment and anxiety (which will be secondary outcomes) and potential mechanisms of action. All variables will be examined and tested for distributional assumptions prior to statistical analysis. We will use within-subject t-tests, separated by treatment group. In this study, these analyses should be considered exploratory. Any data that violates statistical assumptions will either be transformed accordingly and appropriate statistical tests will be applied (e.g., non-parametric approaches such as the Wilcoxon signed rank test in lieu of t-tests). We will look at outcomes for the entire group of enrolled participants for Phase 2 and Phase 3. In addition, in Phase 3, we will examine outcomes for 2 sets of subgroups:

c. Study A vs. Study B
d. Pre-COVID enrollment (including those who participated in some in-person and some video classes, which is the majority of the Pre-COVID enrolled group) vs. Post-COVID enrollment (i.e., those who consented and started video-based classes from the start).

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10. DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

Participants will directly enter self-report data into REDCap, and data collected as part of an interview will be written on a paper CRF and double-entered into REDCap. For the RCT (Phase 3), there will be two REDCap databases – a "blind" database and a "nonblind" database. As described in the assessment table, some assessments are described as being collected by a blind evaluator (research assistant), whereas some are not (because these assessments, by their nature, would break the blind.) There will also be a database that we will use for tracking participants.

Any data, forms, reports, audiorecordings, and other records that leave the site will be identified only by a participant identification number (Study ID, SID) to maintain confidentiality. All paper records will be kept in a locked file cabinet. All data collected will be entered into an electronic database which is stored on a secure server (REDCap) that is backed up on a daily basis. Participant identifying information will be stored in a separate database and will be password protected and stored on a secure server. Care New England's instance of REDCap has been deemed HIPAA compliant by CNE Information Technology.

10.2 Data Management

All self-report data will be collected via REDCap. Interviews (e.g., MINI, QIDS) have standardized forms which we will use and which will be double-entered into REDCap. Any discrepancies will be resolved by the Project Manager in consultation with the MPIs as needed.

Please see also "Data Handling and Record Keeping" in the DSMP.

10.3 Quality Assurance

10.3.1 Training

All research personnel, including yoga instructors will have formal training in research with human subjects (e.g., CITI training, NIH Human Subjects training). Drs. Yen, Uebelacker, Wolff, and Caviness will provide training to and supervise research assistants. Research assistants will also have training in Good Clinical Practice. MPIs and Dr. Wolff will provide training on the MINI and QIDS through didactic teaching, role plays, and feedback on audiotaped sessions. Dr. Uebelacker will provide training and supervision to yoga instructors, and CBT group leaders. Ms. Conti (our lead yoga instructor) will assist with yoga instructor training and supervision.

10.3.2 Quality Control Committee

Drs. Uebelacker, Yen, Wolff, and Caviness will be responsible for quality control of this study. They review recruitment and retention reports, and AE reports, on weekly basis.

10.3.3 Metrics

QIDS Reliability

Research assistants will be trained to administer the QIDS and will be considered certified once they rate 5 practice QIDS to a gold standard rating with an ICC of .80 or greater for total scores. Subsequently, Dr. Yen, Wolff, or Uebelacker will rate 10% of all QIDS administered. Significant discrepancies (greater than 2 for the total score) will be grounds for re-training.

10.3.4 Protocol Deviations

During weekly study meetings, protocol deviations will be discussed with the MPIs, including plans for corrective action. Dr. Caviness will also be alerted to deviations as they occur and will alert the MPIs for any deviation requiring immediate action. Protocol deviations will be logged on the protocol deviation tracking sheet and filed in the regulatory binder.

All assessment time points have a window of time for completion. However, typically due to circumstances outside of the control of the research staff, assessments occasionally occur outside of that window. Assessments that occur outside of the recommended window for completion will be considered to be protocol deviations, and will be logged as such.

Protocol deviations will be reported to NCCIH once per year, in the annual review. The SMC will also receive a list of protocol deviations in their interim or annual reports. Per Butler Hospital IRB policy, "major protocol deviations/violations, defined as those which increase risk to participants" will be reported promptly to the IRB and no more than 10 working days after the investigator is aware of the event. Minor protocol deviations do not need to be reported.

10.3.5 Monitoring

Dr. Caviness (or Dr. Uebelacker, in her absence) will inspect BL documents (consent forms, release of information) for completeness within a week after they are signed. Dr. Caviness will also conduct protocol and data quality monitoring twice a year using the Quality Management review checklists. During Phase 2, all participant and other study records will be reviewed. During Phase 3, a random sample or 15-20% of participant and study records will be reviewed at each monitoring time point.

11. PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

This protocol and the informed consent documents and any subsequent modifications will be reviewed and approved by the IRB or ethics committee responsible for oversight of the study. The consent form should be separate from the protocol document.

11.2 Informed Consent Forms

A signed consent form will be obtained from each participant (adolescent or parent/legal guardian) aged 18 or older. For participants who cannot consent for themselves (i.e, adolescents aged 17 or younger), the parent/legal guardian must sign the consent form, and the adolescent will sign an assent form. The consent/assent forms will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy will be given to each participant and parent/legal guardian and this fact will be documented in the participant's record. When an e-signature is used, we will follow procedures outlined by the Butler Hospital IRB for obtaining that signature.

11.3 Participant Confidentiality

Any data, forms, reports, audio recordings, and other records that leave the site will be identified only by a participant identification number (Study ID, SID) to maintain confidentiality. All paper records will be kept in a locked file cabinet. All data collected will be entered into an electronic database which is stored on a secure server (REDCap) that is backed up on a daily basis. Participant identifying information will be stored in a separate database and will be password protected and stored on a secure server. Care New England's instance of REDCap has been deemed HIPAA compliant by CNE Information Technology.

Information will not be released without written permission of the participant, except as necessary for monitoring by IRB, the FDA, the NCCIH, and the OHRP.

11.4 Study Discontinuation

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

12. COMMITTEES

There will be a Data and Safety Monitoring Board.

13. PUBLICATION OF RESEARCH FINDINGS

Drs. Yen and Uebelacker will be responsible for oversight and approval of any publications or presentations that arise from this research.

14. REFERENCES

1. Mojtabai, R., M. Olfson, and B. Han, *National Trends in the Prevalence and Treatment of Depression in Adolescents and Young Adults.* Pediatrics, 2016. **138**(6).

2. Larson, K., et al., *Trends in Access to Health Care Services for US Children: 2000–2014.* Pediatrics, 2016. **138**(6).

3. Weersing, V.R., et al., *Evidence base update of psychosocial treatments for child and adolescent depression.* Journal of Clinical Child & Adolescent Psychology, 2016: p. 1-33.

4. Iyengar, B.K.S., *Light on the Yoga Sutras of Patanjali*. 1993, London: The Aquarian Press.

5. Cramer, H., et al., *A systematic review and meta-analysis of yoga for low back pain.* The Clinical Journal of Pain, 2013. **29**(5): p. 450-460.

6. Prathikanti, S., et al., *Treating major depression with yoga: A prospective, randomized, controlled pilot trial.* PLoS One, 2017. **12**(3): p. e0173869.

7. de Manincor, M., et al., *Individualized Yoga for Reducing Depression and Anxiety, and Improving Well-Being: A Randomized Controlled Trial.* Depress Anxiety, 2016. **33**(9): p. 816-28.

8. Uebelacker, L.A., et al., *A randomized controlled trial of adjunctive yoga vs. health education for persistent major depression.* Psychological Medicine, in press.

9. Goldstein, N.E., et al., *Guidelines for adapting manualized interventions for new target populations: a step-wise approach using anger management as a model.* Clinical Psychology: Science and Practice, 2012. **19**(4): p. 385-401.

10. Stirman, S.W., et al., *Development of a framework and coding system for modifications and adaptations of evidence-based interventions.* Implementation Science, 2013. **8**(1): p. 65.

11. Weersing, V.R., et al., *Evidence Base Update of Psychosocial Treatments for Child and Adolescent Depression.* J Clin Child Adolesc Psychol, 2017. **46**(1): p. 11-43.

12. Rush, A.J., et al., *An Evaluation of the Quick Inventory of Depressive Symptomatology and the Hamilton Rating Scale for Depression: A Sequenced Treatment Alternatives to Relieve Depression Trial Report.* Biol Psychiatry, 2005.

13. Rush, A.J., et al., *The 16-item Quick Inventory of Depressive Symptomatology (QIDS) Clinician Rating (QIDS-C) and Self-Report (QIDS-SR): a psychometric evaluation in patients with chronic major depression.* Biological Psychiatry, 2003. **54**: p. 573-583.

14. Bernstein, I.H., et al., *Psychometric properties of the Quick Inventory of Depressive Symptomatology in adolescents.* Int J Methods Psychiatr Res, 2010. **19**(4): p. 185-94.

15. American College of Obstetricians and Gynecologists, *Physical activity and exercise during pregnancy and the postpartum period.* Obstet Gynecol, 2015. **126**: p. e135-42.

16. Arsarnow, J., et al., *Stress and Your Mood: A Manual for Groups*. 1999, Youth Partners in Care.

17. Devilly, G.J. and T.D. Borkovec, *Psychometric properties of the credibility/ expectancy questionnaire.* Journal of Behavior Therapy and Experimental Psychiatry, 2000. **31**: p. 73-86.

18. Nguyen, T.D., C.C. Attkisson, and B.L. Stegner, *Assessment of patient satisfaction: development and refinement of a service evaluation questionnaire.* Evaluation and Program Planning, 1983. **6**(299-313).

19. Levine, J.L. and N.R. Schooler, *SAFTEE: a technique for the systematic assessment of side effects in clinical trials.* Psychopharmacology Bulletin, 1986. **22**: p. 343-381.

20. Sheehan, D.V., et al., *Reliability and validity of the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID).* J Clin Psychiatry, 2010. **71**(3): p. 313-26.

21. Kroenke, K., R.L. Spitzer, and J.B.W. Williams, *The PHQ-9: Validity of a brief depression severity measure.* J Gen Intern Med, 2001. **16**: p. 606-613.

22. Beck, A.T., R.A. Steer, and G.K. Brown, *Beck Depression Inventory-II manual*. 1996, San Antonio, TX: Psychological Corporation.

23. Bird, H.R., et al., *The Columbia Impairment Scale (CIS): Pilot findings on a measure of global impairment for children and adolescents.* International Journal of Methods in Psychiatric Research, 1993. **3**(3): p. 167-176.

24. Muris, P. and P. Steerneman, *The revised version of the Screen for Child Anxiety Related Emotional Disorders (SCARED--R): first evidence for its reliability and validity in a clinical sample.* Br J Clin Psychol, 2001. **40**(Pt 1): p. 35-44.

25. Birmaher, B., et al., *Psychometric properties of the Screen for Child Anxiety Related Emotional Disorders (SCARED): a replication study.* J Am Acad Child Adolesc Psychiatry, 1999. **38**(10): p. 1230-6.

26. Hanish, A.E., D.C. Lin-Dyken, and J.C. Han, *PROMIS Sleep Disturbance and Sleep-Related Impairment in Adolescents: Examining Psychometrics Using Self-Report and Actigraphy.* Nurs Res, 2017. **66**(3): p. 246-251.

27. Lau, M.A., et al., *The Toronto Mindfulness Scale: development and validation.* J Clin Psychol, 2006. **62**(12): p. 1445-67.

28. Neff, K.D., *The development and validation fo a scale to measure self-compassion.* Self and Identity, 2003. **2**: p. 223-250.

29. Neff, K.D. and P. McGehee, *Self-compassion and psychological resilience among adolescents and young adults.* Self and Identity, 2009. **9**: p. 225-240.

30. Craig, C.L., et al., *International physical activity questionnaire: 12-country reliability and validity.* Med Sci Sports Exerc, 2003. **35**(8): p. 1381-95.

31. Posternak, M.A., et al., *Assessing past treatment history: test-retest reliability of the Treatment Response to Antidepressant Questionnaire.* J Nerv Ment Dis, 2004. **192**(2): p. 95-102.

32. Farmer, E.M., et al., *Reliability of self-reported service use: Test-retest consistency of children's responses to the Child and Adolescent Services Assessment (CASA).* Journal of Child and Family Studies, 1994. **3**: p. 307-325.

33. Miranda, J., et al., *Development of a patient-report measure of psychotherapy for depression.* Adm Policy Ment Health, 2010. **37**(3): p. 245-53.

34. Crabtree, B.F. and W.L. Miller, *Using codes and code manuals: a template organizing style of interpretation*, in *Doing Qualitative Research, 2nd edition*, B.F. Crabtree and W.L. Miller, Editors. 1999, Sage Publications: Thousand Oaks, CA. p. 163-177.

15. SUPPLEMENTS/APPENDICES

None.