A Pragmatic Clinical Trial of the WE BEAT Well-Being Education Program in Adolescent Congenital Heart Disease: **WE BEAT CHD** Study

PROTOCOL

Version Number: **VERSION 1.0**
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Funded by
The National Heart, Lung, and Blood Institute (NHLBI)
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1. GENERAL INFORMATION

1.1 Protocol Synopsis

Title	A Pragmatic Clinical Trial of the WE BEAT Well-Being Education Program in Adolescent Congenital Heart Disease: WE BEAT CHD Study
Study Objectives	To improve access to preventative, promotive, evidence-based psychosocial care through a telemedicine-based resiliency-building intervention, WE BEAT, in adolescent congenital heart disease (CHD) and create a data repository for the study of associations between self-reported psychosocial health, cardiac health, and biomarkers.
Significance	Adolescents with moderate and severe CHD experience considerable risk of mental health comorbidities. Psychological health is important to cardiovascular health and related outcomes. Access to mental health care, however, is limited, particularly for youth from historically disadvantaged backgrounds and for those with subclinical emotional and behavioral health concerns. There have been few psychological interventions specific to adolescent CHD. This study will evaluate the effectiveness of a resilience and well-being-focused telemedicine intervention in adolescents with CHD and provide one of the largest linkages of adolescent self-reported psychosocial data with cardiac clinical outcomes.
Study Design	This is a 2-arm, 2-staged stratified randomized, parallel, multi-center pragmatic trial in a sample of 390 12-17-year-olds with moderately or severely complex CHD.
Primary Aim	To evaluate the effectiveness of the WE BEAT telemedicine intervention compared to usual care on self-reported resiliency and related psychosocial outcomes.
Secondary Aim(s)	1) To determine associations between self-reported psychosocial survey data and clinical outcomes. 2) To establish the WE BEAT CHD biorepository to study self-reported psychosocial data and stress-related biomarkers.
Accrual	N=390; 300 participants in the intervention arm and 90 in usual care
Study Duration	Approximately 5 years (6-12 months for study start-up; 3 years for enrollment and study follow-up; 1 year for analysis and dissemination).
Inclusion Criteria	• Age 12-17 years old • CHD of moderate or severe complexity (Class II/III, 2018 AHA/ACC ACHD, Table 4) • English or Spanish language proficiency • Receives cardiology care at a PHN or PHN auxiliary site • Parent or guardian and participant willing to comply with protocol and provide written/electronic informed consent and assent
Exclusion Criteria	• CHD of mild or simple complexity (Class I, 2018 AHA/ACC ACHD, Table 4) • Prior heart transplant to treat CHD • Heart disease that is not classified as structural CHD (e.g., connective tissue disease, genetic cardiomyopathy, or acquired heart disease) • Cognitive or developmental conditions that limit program participation and/or ability to complete self-reported measures as determined by a primary cardiology clinician • Suicidality, homicidality, or psychosis in the past 12 months as per medical chart review, clinician report, or eligibility screening • Medically unable to participate (e.g., intubated, unable to respond verbally, active delirium)

1.2 Table of Contents

1.3 List of Figures

1.4 Protocol Version Log

Version Number	Version Date	Comment(s)
Version 0.1	17 FEB 2025	Initial version posted for PHN Protocol Review Committee review.
Version 0.2	01 MAY 2025	Incorporated PRC feedback: clarified exploratory nature of booster session hypothesis, added community service hours to the participant compensation plan, increased dropout rate to a cumulative 30% (baseline to Week 18); modified intervention adherence target, and elaborated on interim analysis and stopping rules. Approved by PRC. Initial version posted for PHN Data Safety Monitoring Board review.
Version 0.3	30 JUN 2025	Incorporated DSMB feedback: clarified assessment of cognitive ability and suicidality exclusion criteria, clarified how suicide-risk would be identified/addressed as part of safety plan, added study flow diagram, streamlined language around intervention description, sample size, interim analysis, and throughout protocol. Added list of figures.
Version 1.0	01 SEP 2025	Minor/administrative edits; no significant changes to content. First version submitted to CCHMC sIRB.

1.5 Table of Revisions

(for future version change control)

1.6 List of Abbreviations

Common abbreviations are listed in tabular format below.

ACC	American College of Cardiology
ACHD	Adult Congenital Heart Disease
AE	Adverse Event
AHA	American Heart Association
ASQ	Ask Suicide-Screening Questions Toolkit
CD-RISC©	Connor-Davidson Resilience Scale
CHD	Congenital Heart Disease
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DCC	Data Coordinating Center
DMP	Data Management Plan
DSMB	Data and Safety Monitoring Board
eConsent	Electronic Consent
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GUID	Global Unique Identifier
HRQOL	Health-Related Quality of Life
ICF	Informed Consent Form
ICH	International Conference of Harmonization
IRB	Institutional Review Board
K6	Kessler-6
LE8™	Life's Essential 8™
MedDRA	Medical Dictionary for Drug Regulatory Activities
MM	Medical Monitor
NHLBI	National Heart, Lung and Blood Institute
NIH	National Institutes of Health
PedsQL™	Pediatric Quality of Life Inventory™
PHN	Pediatric Heart Network
PI	Principal Investigator
PROMIS®	Patient-Reported Outcomes Measurement Information System®
QA	Quality Assurance
QC	Quality Control
QOL	Quality of Life
RRC	Recruitment and Retention Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
UC	Usual Care
WBC	WE BEAT CHD Study
WE BEAT	Wellbeing Education Program: Breathe, Energize, Adjust, Thank

2. STUDY AIMS AND HYPOTHESES

2.1 Primary Aim

To evaluate the effectiveness of the WE BEAT (Wellbeing Education Program: Breathe, Energize, Adjust, Thank) telemedicine intervention compared to usual care on psychosocial outcomes in adolescents ages 12-17 years with congenital heart disease (CHD) of moderate or severe complexity through a 2-arm, 2-staged stratified randomized, parallel, multi-center pragmatic trial.

2.1.1 Hypothesis 1

Participants randomized to the intervention arm will experience greater improvements in self-reported resiliency compared to participants in the usual care (UC) arm.

Primary Outcome: Change in participant self-reported resiliency as measured by the Connor-Davidson Resilience Scale© (CD-RISC©) from baseline to Week 5.[a]

Secondary Outcomes: Change in participant self-reported quality of life (QOL) as measured by the Pediatric Quality of Life Inventory™ (PedsQL™), general distress as measured by the Kessler-6 (K6), life satisfaction, meaning/purpose in life, and depressive/anxiety symptoms as measured by the National Institutes of Health (NIH) Patient-Reported Outcomes Measurement Information System® (PROMIS®) scales, and adolescent lifestyle behaviors as measured by Life's Essential 8™ (LE8™) from baseline to Week 5.[a]

2.1.2 Hypothesis 1A

Participants randomized to the intervention arm will maintain gains in self-reported resiliency compared to participants in the UC arm.

Primary Outcome: Change in participant self-reported resiliency (CD-RISC©) from baseline to Weeks 18 and 30, respectively.[a]

Secondary Outcomes: Change in participant self-reported QOL (PedsQL™), general distress (K6), life satisfaction, meaning/purpose, depressive/anxiety symptoms (PROMIS®), and adolescent lifestyle behaviors (LE8™) from baseline to Week 18 and Week 30, respectively.[a]

2.1.3 Hypothesis 1B

Intervention arm participants randomized to the booster session at Week 18 (~3 months after intervention) will maintain larger gains in self-reported resiliency compared to intervention arm participants without the booster session.

Primary Outcome: Change in participant self-reported resiliency (CD-RISC©) from baseline to Weeks 18 and 30, respectively.[a]

[a] Parent-reported surveys of adolescent psychosocial outcomes will be optional and collected when available.

2.1.4 Hypothesis 2

The WE BEAT telemedicine intervention will demonstrate feasibility and acceptability among participants randomized to the intervention arm as measured by program adherence and overall program satisfaction rating at Week 5.

Primary Outcomes: Participant adherence will be defined as 70% overall session attendance (all participants) and 60% within-participant attendance for WE BEAT sessions (3 of 5 sessions). Overall program satisfaction will be defined as a mean rating of ≥7/10 on the WE BEAT Program participant survey.

Secondary Outcomes: Session ratings, open-ended program feedback, and additional program information collected via the WE BEAT program survey.

2.1.5 Hypothesis 3

Perceived social support and family finances are expected to modify the effect of the WE BEAT intervention on self-reported psychosocial outcomes among intervention arm participants, such that those with lower levels of perceived social support at baseline will experience greater intervention effects, while those with lower family financial means at baseline will experience lesser intervention effects.

Primary Outcome: Change in participant self-reported resiliency (CD-RISC©) from baseline to Week 5.[a]

Secondary Outcome: Change in participant self-reported QOL (PedsQL™), general distress (K6), life satisfaction, meaning/purpose, depressive/anxiety symptoms (PROMIS®), and adolescent lifestyle behaviors (LE8™) from baseline to Week 5.[a]

Primary Predictors: Multidimensional Scale of Perceived Social Support and family finances (income, household structure, marital status, makes ends meet).

2.2 Secondary Aim 1

To develop a data repository to examine associations between participant-reported psychosocial survey data, cardiac clinical factors gathered via medical chart extraction and registry-linkage, and family, social, and community factors.

2.2.1 Hypothesis 1

Participant self-reported resilience, general distress, and depressive/anxiety symptoms will be associated with cardiac outcomes.

Primary Outcome: Composite event score (all-cause mortality or non-elective cardiovascular hospitalization).

Secondary Outcomes: Emergency room visits, hospital days, heart failure (NT-proBNP), metabolic markers (blood glucose/lipids) and participant-reported QOL (as measured by PedsQL™).

Primary Predictors: Participant self-reported resilience (CD-RISC©), general distress (K6), depressive/anxiety symptoms (PROMIS®), and single-item self-perceived health status assessment.

Secondary Predictors: Parent-reported surveys of adolescent resilience, general distress, depressive/anxiety symptoms, and perceived adolescent health status.

2.3 Secondary Aim 2

To examine the impact of the WE BEAT intervention on stress response pathways and assess the effect of baseline physiologic stress on individual response to the intervention through development of the WE BEAT biorepository. Hair, saliva, urine, and blood specimens will be collected from study participants. Urine and blood specimens will be optional.

2.3.1 Hypothesis 1

Participant-reported resilience, general distress, and depressive/anxiety symptoms will be associated with biomarkers of stress that may help quantify the physiologic impact of psychosocial stressors and predict and track the intervention response.

Primary Predictors: Hair cortisol and cortisone levels will be assayed from hair samples collected at baseline, Week 5, and Week 30 to assess change over time in response to the intervention and usefulness in predicting participant response.

Secondary Predictors: Since chronic stress can affect inflammation and accelerate aging, markers of inflammation (CRP, TNF alpha, and IL-6) and epigenetic markers of aging (from genome-wide epigenetic profiling) will be collected from saliva samples collected at baseline, Week 5, and Week 30.

3. BACKGROUND INFORMATION

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

Psychological Health in Pediatric Congenital Heart Disease (CHD). Recent national prevalence rates indicate that approximately 1 in 6 children and adolescents in the United States experience a mental health disorder, with approximately half of these youth not receiving necessary mental health treatment.[1] A National Emergency in Youth Mental Health was declared in October 2021 by leading pediatric and psychiatric societies. This was prompted by a doubling in youth depressive and anxiety symptoms seen globally.[2] Children with CHD experience even greater risk of mental health concerns. In a comparative cross-sectional analysis study, it was found that children with simple CHD had a 5 times greater odds of treatment or diagnosis of anxiety or depression than children without CHD, while those with single ventricle CHD had 7 times greater odds compared to healthy peers.[3] Two-thirds of pediatric patients with single ventricle CHD will experience a mental health condition, such as depression or anxiety, in their lifetime,[4,5] and these mental health risks continue into adulthood with high rates of mental health diagnoses among the growing adult CHD (ACHD) population.[6]

Gaps in Mental Health Care in Pediatric CHD. Family, social, and community factors have contributed to a widening mental health gap between children from households with fewer resources when compared to those with higher financial status.[7] CHD patients of minority race and those without private insurance have lesser odds of receiving a diagnosis of a mental health condition and/or receiving treatment when compared to non-Hispanic White peers.[3,8] Additionally, there remains a critical gap in the development, implementation and testing of psychological interventions in CHD.[9,10,11] A recent review identified only four studies of psychological interventions in youth with CHD, all of which were limited in efficacy.[12] Through an international study of over 1200 patients/caregivers with pediatric heart disease, 30% of respondents indicated a desire for more access to mental health/self-care information while nearly 1 in 4 stated a need for increased access to psychology/therapy services, as well as support groups.[13] In a recent preliminary analysis of a Pediatric Heart Network (PHN) dataset, more than half of parents of children with single ventricle CHD endorsed having concerns about their child's mental health (McCormick et al., unpublished data).

Psychological Health and Cardiac Outcomes. Lack of access to specialized mental health care has the potential to impact medical and cardiac outcomes. Associations between psychological health and adult cardiovascular outcomes, such as mortality and hospitalizations, have been established.[14] In a sample of adults with CHD, a diagnosis of depression was found to be associated with inflammation (hsCRP), heart failure (NT-proBNP), all-cause mortality, and composite outcome of death or non-elective cardiac hospitalization.[15] Similarly, in multi-variate models, depression was found to be a significant driver of perceived health status in adults with CHD, even more so than cardiac-specific variables.[16] Among a single-center sample of adults with moderate or severe CHD, depressive symptoms and self-efficacy were associated with self-care behaviors (i.e., health behaviors, symptom monitoring and management) in multi-variate modeling.[17] While there has been limited study of self-reported psychological health and cardiac outcomes in pediatric CHD, the broader child health literature underscores the importance of such investigation. Childhood adversities known to be prevalent in CHD populations, including negative life events (i.e., hospitalizations, surgeries, impact on activities of daily living, family conflict), parental mental health conditions,[18,19] and economic hardship,[20] are drivers of cardiovascular risk, morbidity, and mortality through biological, behavioral and psychological mechanisms (as shown in ***Figure 1***).

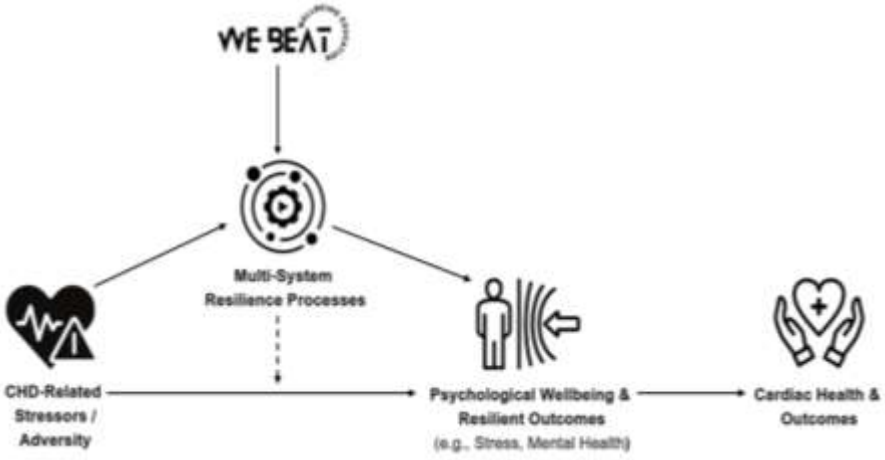

Figure 1. WE BEAT Theoretical Framework

Resilience, Psychological Health, and Cardiac Health. Resiliency has been defined as the process by which an individual harnesses internal, external and learned resources to maintain wellness and wellbeing amidst a stressor.[21] Resilience is conceptualized as a multi-faceted promotive and protective process that is derived from internal and external resources. Further, one's resilience is dynamic, changing and modifiable.[22,23,24] Resilience is associated with important outcomes in general child/adolescent and pediatric chronic illness populations. In a recent systematic review of the general child and adolescent literature, greater resilience was found to be associated with fewer mental health concerns across all studies.[17] Similarly, in recent sample of 332 patients with CHD (M = 17.2 ± 5.1 years), higher self-reported resilience was associated with fewer mental health diagnoses and involvement in CHD peer support communities/camps.[25] Moreover, resiliency has been shown to be associated with improved health-related quality of life in pediatric cancer patients,[26] better glycemic control in adolescents with diabetes,[27] and decreased depressive symptoms in youth with CHD.[28] As shown in ***Figure 1***, we conceptualize resiliency as a modifiable process that serves an important role between the stressors associated with CHD and mental health and related well-being outcomes. This pathway is likely to continue on to impact cardiac health and health behaviors. Interventions targeting resilience across other pediatric chronic illness groups and adult CHD (ACHD) have shown promise at increasing resilience[26,29] and decreasing health-related anxiety[29] and depressive symptoms,[30] with positive effects on resiliency sustained 3 months post-intervention.[29] These intervention studies in pediatric cancer and ACHD also identified areas for improvement in terms of intervention design and delivery. For example, in the ACHD intervention trial, transportation was the biggest barrier to study participation. Only half of the participants attended all 8 study sessions, yet 71% attended at least 4 sessions.[30] The benefits of peer support in adjustment to pediatric chronic illness have been well-established[31] and pediatric CHD patients report a desire for more opportunities for peer-to-peer

connection;[13] however, resilience interventions in pediatric populations have been largely delivered via individual, in-person sessions to-date.[26,32]

Improving Access and Increasing Resilience through the WE BEAT Well-Being Education Program. The WE BEAT Well-Being Education Program was developed for pediatric patients with heart disease.[33] This program was developed by a clinical psychologist with 10+ years of mental health practice with youth with heart disease and serious childhood illness. WE BEAT program development was further informed by a NHLBI-funded (5K23HL45096) semi-structured interview study conducted with representative sample of youth ages 12-24 years of age with advanced heart disease and their caregivers.[34] The evidence-based components of the 5-module WE BEAT intervention, which are described in detail in the design manuscript,[33] are derived from cognitive behavioral theory, stress management and resiliency research, and behavioral intervention science across pediatric populations and adult heart disease. The five WE BEAT modules include: (1) **W**ell-being **E**ducation--Introduction, (2) **B**reathe--Mindfulness and Relaxation-Based Skills, (3) **E**nergize--Positive Psychology Skills, (4) **A**djust--Cognitive Skills Training, and (5) **T**hanks--Gratitude Practice. The overall objective of the WE BEAT CHD Program is to foster positive psychological well-being and resilient outcomes in adolescents with CHD through a mental health promotion and prevention lens while providing access to safe, peer-to-peer community building. Through its group-based telemedicine delivery, the program aims to increase access to mental health care (i.e., provider availability, lack of insurance, need for diagnosis) for the representative population of young people we care for while emphasizing prevention-focused, early mental health intervention.

3.2 Prior Studies

WE BEAT Pilot Study in Fontan CHD. The WE BEAT telemedicine group program was recently piloted in a single-center sample of adolescents 13-18 years old with Fontan-palliated CHD who were also willing to participate in a 6-month individualized exercise training program.[35] Among eligible patients reached, 68% expressed interest in study participation. Of those consented, 77% had been scheduled for a group program at time of analysis with 87% program completion. Twenty adolescents (*mean* age 16.1 ± *SD* 1.6 years) participated in five WE BEAT group cohorts (range: 3-6 participants per group). The majority (80%) attended 4 or 5 sessions in the 5-session program, and the median program satisfaction rating was a 9 out of 10 (10=most favorable rating). Due to the small pilot sample size, an effect size calculation was used. Effect size is a measure of clinical meaningfulness or impact. Even a small effect of an intervention on an identified outcome can have a meaningful clinical impact for an individual. Following WE BEAT participation, resiliency (d=0.44; medium effect size) and perceptions of purpose in life increased (d=0.26; small effect size), while depressive symptoms decreased (d=0.36; medium effect size).

3.3 Rationale for the Study

Adolescents with moderately and severely complex CHD experience considerable risk of mental health comorbidities. Psychological health is important to cardiovascular health and related outcomes. Access to mental health care, however, is limited for many young people and for those with subclinical emotional and behavioral health concerns. There have been few psychological interventions specific to adolescent CHD. This study will evaluate the effectiveness of a resilience and well-being-focused telemedicine intervention, WE BEAT, in adolescents with CHD and provide one of the largest linkages of adolescent self-reported psychosocial functioning, cardiac factors and outcomes, family, social and community factors, and stress, cardiac and genetic biomarkers.

3.4 Rationale for Study Outcomes

Participant self-reported resiliency is the primary study outcome. Higher resiliency is associated with lower levels of depression, anxiety, and stress among adolescents, as well as reduced risk

behaviors.[22,23,24,36] Resilience is modifiable and skills that promote resilience can be taught and fostered, even among those living in higher-risk environments. The intervention was developed to be a preventive and promotive evidence-based psychosocial intervention as opposed to a specific mental health treatment for a presenting mental health concern. Secondary outcomes, including general stress, depression, anxiety, self-perceived illness status, and health behaviors were selected given their associations with resilience and intervention domains (e.g., cognitive skills training, relaxation training).

4. STUDY / TRIAL DESIGN

4.1 Overview

This study will employ a 2-arm, 2-staged stratified randomized, parallel, multi-center pragmatic trial design. Pragmatic trials aim to provide evidence for the adoption of an intervention in the real-world clinical setting.[37] Given that the overall objective of this study is to demonstrate effectiveness of the WE BEAT intervention across diverse sites and participants to increase access to preventative and promotive psychological health intervention, the emphasis on real-world applicability is important. The PRECIS-2 (PRagmatic Explanatory Continuum Indicator Summary-2) tool was used to enhance pragmatism in this trial design, particularly with respect to inclusion/exclusion criteria, study arms (i.e., usual care as comparator), measurement selection (i.e., emphasis on brevity), and intervention delivery.[38]

The study objective is to evaluate the effectiveness of the WE BEAT telemedicine intervention on resiliency and related psychosocial outcomes in adolescents with congenital heart disease (CHD) of moderate or severe complexity, defined as Class II or III in Table 4 of the 2018 American Heart Association (AHA)/American College of Cardiology (ACC) Guidelines for the Management of Adults with CHD. A sample of adolescents with CHD who meet eligibility criteria (refer to **Section 5**) will be recruited across participating PHN sites with stratified randomization to the intervention or UC arm (see ***Figure 2. WE BEAT CHD Study Schematic***). Following completion of the WE BEAT program, intervention arm participants will be randomized to a single booster session at Week 18 vs. no booster session.

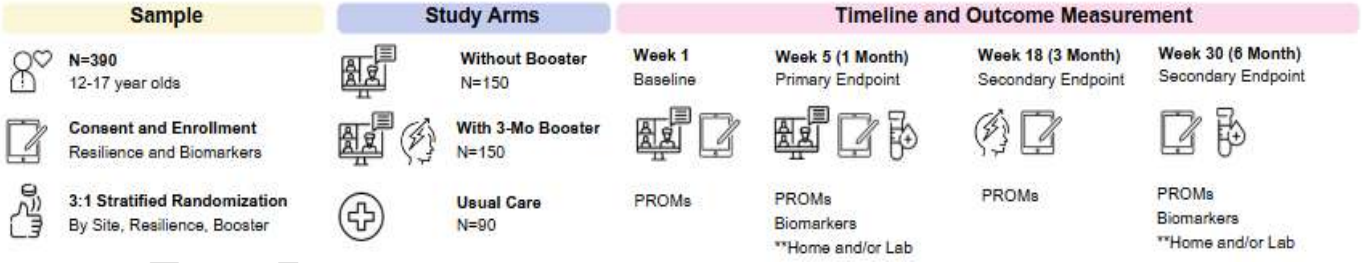

Figure 2. WE BEAT CHD Study Schematic

The primary outcome will be participant self-reported resiliency at Week 5 (i.e. primary endpoint, immediately post-intervention). Follow-up assessments will occur at Weeks 18 (~3 months post-intervention) and 30 (~6 months post-intervention) to allow for the study of intervention maintenance effects. Secondary aims will include the retrospective study of participant-reported psychosocial outcomes with a) cardiac clinical outcomes, b) family, social, and community factors, and c) stress, cardiac, and genetic biomarkers through the development of a WE BEAT CHD biorepository.

4.2 Procedures to Minimize/Avoid Bias

4.2.1 Sample Bias

The PHN sites represent broad geographical coverage with each being national/international referral centers for increased diversity and generalizability within the study sample. This study will employ several strategies to ensure a representative participant sample. Study participation will require access to an electronic device with internet capabilities for participation in the virtual group program. Recent Pew Center national survey data show 95% of U.S. teens have access to a smartphone and 97% report using the Internet daily. This PHN study will provide loaned internet-capable devices and/or prepaid Wi-Fi cards if needed. Patient/family representatives will serve on the PHN Recruitment and Retention Committee (RRC) to help develop best practices and support participant recruitment and retention efforts (see the PHN Manual of Operations for more information). In addition to co-design of recruitment materials and procedures with the PHN RRC, we will employ community-based participatory research practices to study recruitment, enrollment and retention, which have been outlined for clinical trials within pediatric chronic and critical illness populations.[39] In-person, electronic, and phone-based recruitment and consent procedures will be employed.[38,40] Multiple contacts will be made to optimize recruitment of a representative participant sample. Previous research has shown that nearly 10 months and 15 contacts were needed, on average, to recruit a representative sample in a behavioral health clinical trial.[41] English and Spanish electronic consent (e-consent) forms will be available.

Parents/guardians may opt-in to secondary data collection for parent-reported assessment of child psychosocial functioning. However, parent participation in the study is not necessary for participant enrollment in the study. Eliminating the requirement of parent participation in the study increases opportunities to recruit a representative participant sample,[41] as systematic review demonstrates higher participation of youth from lower resourced groups in adolescent-only focused clinical trials.[42]

4.2.2 Generalizability

Based on the recruitment, eligibility, and pragmatic clinical trial design strategies described throughout this protocol, we expect the results of the trial to be generalizable. Additionally, the study population includes participants with both moderately and severely complex CHD to support generalizability of findings and implications. Lastly, the intervention will be delivered by a team of psychologists from three PHN sites, supporting generalizability of intervention delivery.

4.2.3 Randomization

Eligible participants will be randomly assigned to one of two treatment arms: intervention or usual care. Participants will be randomized in a 3:1 ratio (3 in the intervention arm to 1 in the usual care arm) and in the order they are enrolled into the study. Randomization assignments will be generated by a web-based system at the data coordinating center (DCC) to receive the allocated treatment according to a computer-generated randomization plan using the DCC's randomization program, after confirmation of trial eligibility. Once a participant has been assigned a treatment allocation code, the participant will remain in the same study arm for the duration of the study. While randomization does not ensure that any particular baseline characteristic, other than the stratification variable, will be balanced between treatment groups, it does minimize potential for study team members or participants to decide who would receive the WE BEAT intervention. Participants in the intervention arm who complete the intervention program will be further randomized in a 1:1 ratio post-intervention with one group receiving an additional booster session at Week 18.

4.2.4 Stratification

Randomization will occur within strata defined by participant self-reported resilience using the Connor-Davidson Resilience Scale© (CD-RISC©)[43,44] at time of study enrollment. We will stratify participants by high resilience (defined as approximately top 20% of CD-RISC©) and moderate-low resilience (defined as the lower 80% of CD-RISC©) as assessed by their enrollment resilience score. The results of the pilot study suggest that high resilience group could be initially defined as CD-RISC© ≥ 34 (see **Section 8.4** for additional details). The rationale for stratification is based on the results of previous PHN studies suggesting that participants with high baseline scores may have a different pattern of response to the intervention.

Randomization will be also balanced within clinical site so that any site-specific characteristics will be approximately evenly balanced between treatment arms. We acknowledge that usual care as it pertains to psychosocial support and mental health is likely to vary across PHN and auxiliary sites. We will collect institution-level data annually throughout the course of the trial to describe and understand the center-level psychosocial supports available to participants during the course of their study participation.

4.3 Study Measures

All surveys are self-reported measures and will be administered electronically by secure link, email, or in-person via tablet if requested. A research coordinator can aid in completion as needed. Parent reports of adolescent psychosocial outcomes will be optional and collected when available.

4.3.1 Measures of Primary Outcome

Connor-Davidson Resilience Scale© (CD-RISC©).[43,44] 10 items; self-reported, unidimensional 5-point Likert scale measuring resilience. Total scores range from 0-40 with higher scores indicating greater resilience. A modified parent-reported version will also be available. Available in Spanish. The CD-RISC© is one of the most widely used measures of resilience. It has been validated for use in children and adolescents across various countries.[45,46] The CD-RISC© been used in intervention studies targeting resilience in adolescents with cancer[26,32] and was used as the primary outcome measure of the WE BEAT pilot study in Fontan CHD.[35] Time to complete is 1-5 minutes.

4.3.2 Measures of Secondary Outcome(s)

NIH Patient-Reported Outcomes Measurement Information System® (PROMIS®) Scales.[47,48,49] 24 items; self-reported, 5-point Likert scales measuring depressive symptoms (8 items); anxiety (8 items); meaning and purpose in life (4 items); life satisfaction (4 items). Participant- and parent-reported versions available. Available in Spanish. The NIH PROMIS® Scales have been validated for use in children with chronic health conditions ages 8-17 years old[48] and were utilized as the secondary outcomes measures in the WE BEAT pilot study in Fontan CHD.[35] Time to complete is 5-10 minutes.

Kessler-6 (K6).[50] 6 items; self-reported, 5-point Likert scale measuring general distress. Total scores range from 0-24 with higher scores indicating more psychological distress. The K6 is available in 14 languages, including Spanish. The K6 is a widely used, well-validated screening measure of non-specific, general psychological distress over the past 30 days.[51] Time to complete is 2 minutes.[50]

PedsQL™, Generic Core[52] and Cardiac Module.[53] 23 items and 27 items; self-reported; 5-point Likert scale measuring health-related quality of life (HRQOL). Scores will be transformed to a 0-100 scale with higher scores indicating more positive HRQOL. The PedsQL™ Generic Core is widely used and includes four domains: Physical, Emotional, Social, and School functioning. The Spanish version

of the measure was determined to be psychometrically sound in a sample of Spanish speaking youth with CHD.[54] The PedsQL™ Generic has been validated for use in pediatric heart disease populations.[55,56] The PedsQL™ Cardiac Module is administered in addition to the PedsQL™ Generic Core to gather cardiac-specific constructs important to QOL. Subscales include: Heart Problems and Treatment (e.g., symptoms, medical interventions), Treatment Barriers (e.g., difficulty accessing care, adherence with treatment), Perceived Physical Appearance (e.g., concerns related to scars, body image), Treatment Anxiety (e.g., worries about medical procedures and hospital visits), Cognitive Problems (e.g., difficulties in concentrating, memory issues), and Communication (e.g., ability to discuss condition and treatment with others). Both the Generic Core and Cardiac Module take 5-10 minutes to complete (total of 10-20 minutes).

Life's Essential 8™ (LE8™). 8 items; self-reported scoring tool measuring lifestyle behaviors. Items align with the American Heart Association's key metrics for promoting cardiovascular health and overall well-being.[57] Items include assessment of diet, sleep, physical activity, and nicotine use/exposure. This survey has been recommended by the International Consortium for Health Outcomes Measurement as patient-centered outcomes measure for CHD.[58] Time to complete is 1-5 minutes.

Multidimensional Scale of Perceived Social Support.[59] 12 items; self-reported; 7-point Likert scale measuring perceived social support. Available in Spanish.[60] Total score ranges from 1-7 with higher scores indicating more perceived social support. Subscales include: family subscale, friends subscale, and significant other subscale. The psychometric properties of this scale have been established in diverse samples of adolescents.[61,62] Time to complete is 5 minutes.

Self-Perceived Health Status. 1 item; self-reported; linear analog scale. Subjectively perceived health status will be measured with a linear analogue scale ranging from the ''worst imaginable health state'' (score of 0) to the ''best imaginable health state'' (score of 100). This linear analog scale is part of the EuroQol instrument and has been used to measure self-perceived health status in adolescents and young adults with CHD.[63] Time to complete is 1 minute.

WE BEAT Survey. 10 items; self-reported. An investigator-designed survey used to gather WE BEAT session and overall program ratings and acceptability, as well as feedback and ideas for program improvement. Time to complete is 1-5 minutes.

4.3.3 Covariate Measures

Demographics and Family, Social and Community Factors. At study enrollment, the consenting parent/guardian will complete a PHN-designed survey to collect key participant and family demographic information as well as family, social, and community information known to relate to health outcomes. This survey was developed in partnership with the PHN Data Science Committee. Domains include: participant/family neighborhood (GEOID, or geographic identifiers), race/ethnicity, language, employment/school status, health insurance coverage, health costs/barriers, parental marital status and education, household structure, housing stability, family income/finances, spirituality, food security, cell phone access, and social media use.

Mental Health History and Services. At study enrollment, the consenting parent/guardian will complete an investigator-designed survey of child and family mental health history and current mental health services. This survey includes questions regarding current child/family mental health diagnoses, current child/family mental health treatment (i.e., psychotherapy, pharmacologic), past mental health diagnoses, past mental health treatment, current/past serious risk concerns (i.e., suicidality), and child/family mental health needs.

4.4 Study Visits

There will be 5 visits over the course of the study. eConsent and randomization will be completed at the enrollment visit. Surveys will be completed electronically at baseline (Week 0), Week 5, Week 18, and Week 30. Biospecimens will be collected at baseline, Week 5, and Week 30 either on-site at enrolling centers (or approved local laboratory) or by participants at home with biospecimen collection kits (see ***Figure 3. WE BEAT CHD Study Flow Diagram*** and ***Table 1. Schedule of Visits/ Measurements*** for details).

Participants will be compensated for each survey timepoint completed and for each biospecimen provided. In addition, participants who complete the study in its entirety will receive a certificate of completion documenting five community service hours for their time participating in research that is not compensated (e.g., enrollment visit, intervention sessions, additional survey time).

Parents/guardians who choose to complete optional parent-reported surveys will also be compensated for each survey timepoint completed.

Figure 3. WE BEAT CHD Study Flow Diagram

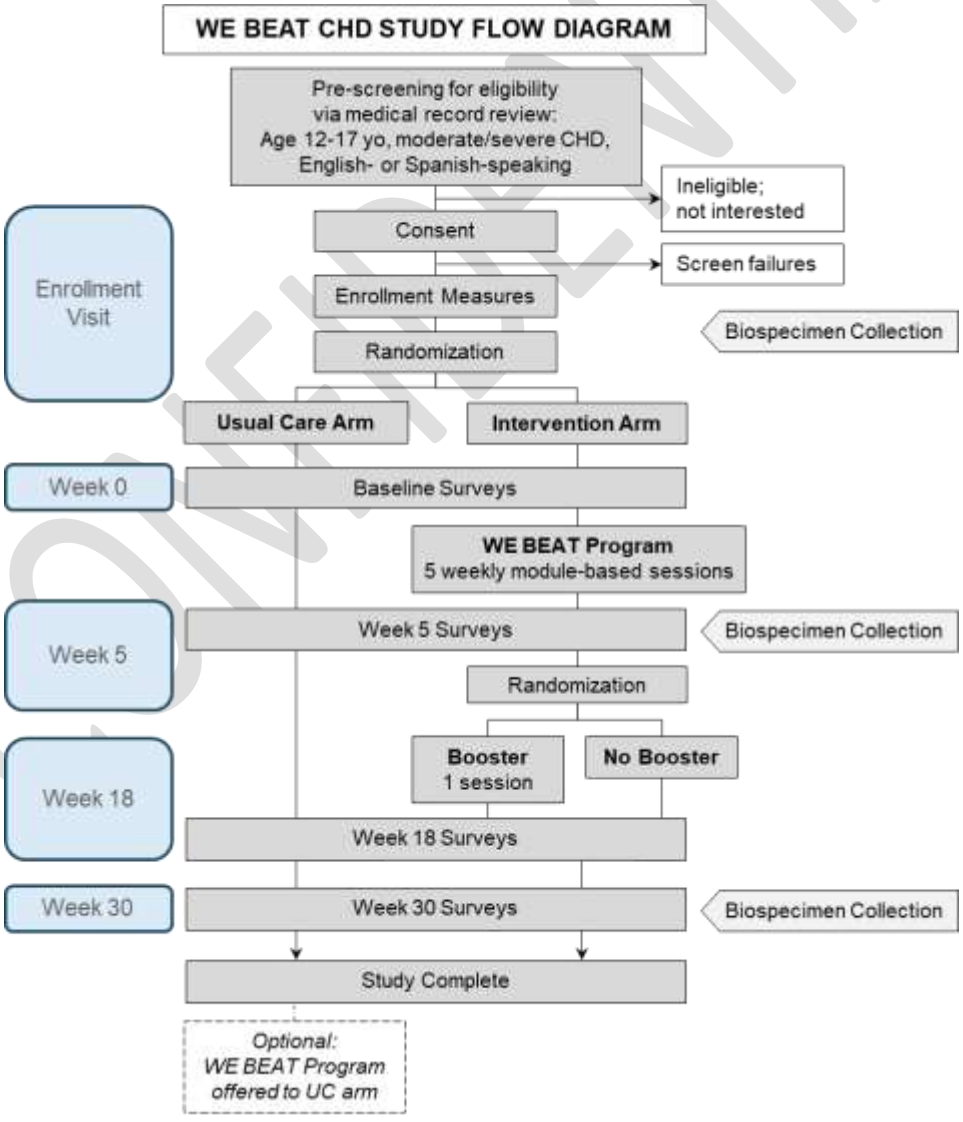

Table 1. Schedule of Visits/Measurements

Study Measure	Reporter	Enrollment	Week 0¥	Weeks 1°-4	Week 5	Week 18	Week 30
ENROLLMENT (ALL)						3 MONTHS POST-INT	6 MONTHS POST-INT
Eligibility	Site	X					
Site Survey	Site	X					
Informed Assent	Participant	X					
Informed Consent	Parent	X					
Demographics, Socioeconomic Status	Parent	X					
Mental Health History	Parent	X					
Randomization	Site	X			X (subset)		
BIOSPECIMENS							
Hair/Saliva Specimens	Participant	X			X		X
Urine Specimens^	Participant	X					
Blood Specimens^	Participant	X			X (subset)		X (subset)
INTERVENTION (INTERVENTION ARM ONLY) ~45 MINUTES PER VIRTUAL SESSION				**WE BEAT SESSIONS 1-5**		**BOOSTER SESSION**	
WE BEAT Program	Participant			X	X		
WE BEAT Survey	Participant				X		
WE BEAT Booster Session	Participant					X (subset)	
SURVEYS (ALL)+			W0		W5	W18	W30
CD-RISC©	Participant*	X	X*		X*	X*	X*
PedsQL™ Generic Core and Cardiac Module	Participant*		X*		X*	X*	X*
NIH PROMIS® Scales	Participant*		X*		X*	X*	X*
Kessler-6	Participant*		X*		X*	X*	X*
Life's Essential 8™	Participant*		X*		X*	X*	X*
Multidimensional Survey of Perceived Social Support	Participant		X		X	X	X
Self-Perceived Illness Severity	Participant*		X*		X*	X*	X*
Estimated Survey Time		*10 minutes*	*60 minutes*	*N/A*	*60 minutes*	*60 minutes*	*60 minutes*
VISIT/SESSION/SURVEY MODALITY		In Person/ Electronic	Electronic/ Virtual	Virtual	Electronic / Virtual	Electronic	Electronic

¥ Week 0 window opens immediately after enrollment for participants randomized to the Usual Care arm, and 10 days prior to Week 1 for participants randomized to the Intervention arm.

° For those randomized to the Intervention arm, Week 1 will start in conjunction with the first session of the WE BEAT program, and therefore will depend on cohort scheduling and availability. Post-intervention study timepoints will be based on the completion of the 5-session program.

^ Participant urine and blood specimens are optional; on-site specimen collection preferred. See study manual for details.

+ In general, surveys should be completed within 2 weeks of due date. See study manual for details.

* Parents who consent to optional surveys will complete parent-reported versions of each survey.

5. SELECTION AND WITHDRAWAL OF PARTICIPANTS

5.1 Participant Inclusion Criteria

a) Ages 12-17 years old
b) CHD of moderate or severe complexity (Class II/III per 2018 AHA/ACC ACHD, Table 4)
c) English or Spanish language proficiency
d) Receives cardiology care at a PHN or PHN auxiliary site
e) Parent or guardian and participant willing to comply with protocol and provide written informed consent and assent

5.2 Participant Exclusion Criteria

a) CHD of mild or simple complexity (Class I)
b) Prior heart transplant to treat CHD
c) Heart disease that is not classified as structural CHD (e.g., connective tissue disease, genetic cardiomyopathy, or acquired heart disease)
d) Cognitive or developmental conditions that limits ability to complete self-reported measures and/or participate in group intervention as determined by a parent/guardian or primary cardiology clinician
e) Suicidality, homicidality, or psychosis in the past 12 months as per medical chart review, clinician report, or eligibility screening
f) Medically unable to participate (i.e., intubated, unable to respond verbally, active delirium)

Cognitive and Developmental Functioning. Cognitive or developmental conditions will be assessed by asking parents/caregivers and cardiology care team about the adolescent's ability to join a group session and complete surveys independently or with minimal assistance (i.e., items read to them but they answer); no diagnoses or intelligence quotient levels will be utilized to exclude participation. It is acceptable for a participant to complete surveys with parent or caregiver assistance.

Suicidality, Homicidality, and Psychosis. Any potential participant with documentation of suicidality (with intent or plan), homicidality, or auditory/visual hallucinations in medical chart or by cardiology clinician report will not be approached for study. At eligibility screening, study staff will screen for suicidality and homicidality using two modified questions from the Ask Suicide-Screening Questionnaire (ASQ):

1. In the past year, have you had thoughts of hurting or killing yourself or others?
2. Have you ever tried to seriously hurt or kill yourself or others?

If a screened participant indicates 'yes' to either, they will be deemed ineligible for the study, and a brief suicide safety assessment will be conducted by a trained clinician at the research site per their local institutional practices (e.g., psychologist, social worker, nurse practitioner, physician assistant, physician, or other mental health clinicians) to determine next steps. Training on these processes and safety protocols will be provided to study PIs and coordinators prior to site activation by the study chair and/or other clinical psychologist and will also be detailed thoroughly in the study manual. A resource list will be provided to all participating sites. Throughout study participation, any report of suicidality will be recorded as an adverse event according to standard safety reporting procedures (**Section 7**). Upon completion of the study, sites will be asked to report if new concerns or reports of suicidality or homicidality presented during the course of the study for both intervention and UC arm participants.

5.3 Participant Withdrawal Criteria

5.3.1 Discontinuation of Study Treatment

Participants may be withdrawn from the study for the following reasons:

- Participant (or legal guardian) declines further study participation.
- In the investigator's, interventionist's or primary cardiology clinician's judgment, it is in the participant's best interest.
- Change in medical, cognitive, developmental or psychiatric status now meeting study exclusion criteria or resulting in inability to participate in intervention sessions.

5.3.2 Participant Withdrawal from Study

If the participant refuses to continue with the study visits, every attempt should be made to continue contact by telephone, written communication, or record review to determine if outcome events have occurred, unless the participant specifically refuses such follow-up. The reason for withdrawal will be documented for all participants withdrawn from the study.

5.4 Participant Availability

Study participants will be enrolled from the Pediatric Heart Network, including the 9 PHN core sites/consortia (consisting of 12 institutions). A review of surgical procedures, medical records, and clinic volume was performed to confirm each institution's ability to recruit 32-33 participants during the enrollment period to reach the planned sample size. Additional PHN auxiliary sites will be onboarded as needed to bolster recruitment.

Identifying Eligible Participants. Eligible participants will be identified by the site principal investigator (PI), research coordinator, or PI designee via review of inpatient census and weekly outpatient clinic schedules of clinicians who care for patients with moderately to severely complex CHD. A member of the research team will approach the parents of patients meeting all inclusion criteria with no known exclusion criteria to discuss eligibility and participation. Additionally, cardiology clinicians can refer patients to the study for consideration of eligibility and participation. In collaboration with the PHN RRC, recruitment materials (fliers, postcards) will also be created and distributed to facilitate recruitment and encourage patients/families to self-identify as eligible and interested.

5.5 Recruitment / Enrollment Procedures

Consent Procedures. Study consent and enrollment will occur in-person at the enrolling site in accord with other clinic visits, or virtually. eConsent and assent forms will be available in English and Spanish. A member of the research team will explain the trial and ensure that parents/participants have ample opportunity to read the consent form and any study documents, taking time to review details and answer questions. Parents/guardians will provide e-consent, and participants will provide electronic assent. Enrollment measures will be completed electronically at the baseline visit by participants and parent/guardian as indicated (see ***Table 1. Schedule of Visits/Measurements***).

Study Communication. Communication with enrolled participants will occur via parents/guardians for study coordination and survey completion using multiple methods, including phone calls, study emails, text messages, and HIPAA-compliant messaging in the study data capture platform. When permitted by parent/guardian, a participant email and/or text can also be sent in accord with those sent to parent/guardian. Site research coordinators will assist with reminders and follow-up to support data collection and completion for up to 12 months after study enrollment.

6. TREATMENTS TO BE ADMINISTERED

6.1 Description of Study Treatments

Participants will be randomized to one of two treatment arms: Usual Care or Intervention. Usual care (UC) will be defined as the standard psychosocial treatment or management practices that are typically provided to patients at their care center outside of a research study. Participants randomized to the intervention arm will receive the WE BEAT intervention program (described in **Section 3**).

WE BEAT Telemedicine Group Program.[33] Intervention arm participants will be placed in a WE BEAT group cohort based on schedule preference and availability. Group cohorts of approximately 10 participants across enrolling sites will be developed on a rolling basis.

The program will be delivered over five weekly 45-minute sessions. The five WE BEAT modules that will be covered include: (1) Wellbeing Education, Introduction, (2) Breathe, Mindfulness and Relaxation-Based Skills, (3) Energize, Positive Psychology Skills, (4) Adjust, Cognitive Skills Training, and (5) Thanks, Gratitude Practice (see ***Table 2. WE BEAT Program Modules***). Each module was developed based on supporting resilience theory and evidence, as referenced in Table 2. An accompanying WE BEAT workbook will be provided to program participants.

Table 2. WE BEAT Program Modules

Session	Module	Supporting Theory and Evidence[14, 64, 65, 66]	Skills Taught
1	Introduction	Resources; Social Support / Peer Connection[31, 67, 68]	Introduction to Program and Community Building
2	Breathe	Assets; Relaxation, Mindfulness [69, 70, 71]	Diaphragmatic Breathing, Guided Imagery, Word Focus Meditation
3	Energize	Assets; Purpose in Life, Positive Psychology[72]	Finding Purpose, Pleasant Events/Passions, Movement/Exercise
4	Adjust	Assets; Cognitive Skills,[73, 74] Optimism[75]	Thought Challenge, Self-Talk, Radical Acceptance
5	Thank	Assets and Resources; Gratitude[75, 76, 77, 78]	Others Gratitude, Self-Gratitude, Heart Journey Gratitude
6	Booster		Review of Modules 2-5

WE BEAT group sessions will be conducted via a HIPAA-compliant electronic meeting platform, such as Zoom, etc. Reminders and meeting links will be disseminated electronically to participants prior to each session.

Session Format. Each WE BEAT session follows the same outline: (I) Welcome/Check-In/Review (10 minutes), (II) Evidence (i.e., developmentally appropriate overview of science related to session; 5-10 minutes), (III) Instruction in three skills/activities (15-20 minutes), and (IV) Goal Setting and Wrap-Up (5-10 minutes). Each session includes a review of topics and skills covered in the previous weekly session, and skill practice between sessions will be encouraged. The WE BEAT workbook follows along with each telemedicine-based session, providing written overview/instruction in each of the skills as well as goal setting and reflective prompts. Following each weekly session, participants will

receive an electronic reminder to review the previously covered module and skills. This post-session notification will include links to videos or other resources shared during the previous session for all participants to reference. See **Section 6.3** for information on monitoring intervention adherence and resources for missed sessions.

Booster Session. Following completion of the primary WE BEAT intervention at Week 5, intervention arm participants will be randomized to a single-session booster session (occurring at Week 18) vs no booster session. Intervention arm participants who missed more than 2 program sessions will not be eligible for the booster. The booster session will be provided in a similar format to the WE BEAT program. A review of all modules/skills introduced in the program will be provided. Participants will be encouraged to discuss and reflect on what skills they have utilized and barriers they have encountered to putting skills into practice.

Intervention Core: Delivery and Treatment Fidelity. The NIH Behavior Change Consortium (NIH BCC)[79] emphasizes the importance of maintaining intervention fidelity to ensure reliable and valid outcomes in behavioral health research. The NIH BCC recommendations for enhancing treatment fidelity in behavioral health research informed the development of intervention delivery and training.

The University of Michigan will serve as the Intervention Core Lead under the direction of study chair and intervention developer, Melissa Cousino, PhD. The Intervention Core Lead will maintain program materials, develop language translations, and work with the program's design team if additional materials are needed (i.e., retention postcards). In addition to Dr. Cousino, interventionists selected from three U.S. sites representing the West, Midwest, and Northeast will join the Intervention Core to deliver and facilitate the telemedicine program. Interventionists undergoing facilitator training must hold an independent license for the practice of psychology in their state.

Initially, interventionists will complete a 1-day in-person training program led by the study chair using the standardized WE BEAT intervention manual which details session content and delivery procedures. The training will emphasize theoretical underpinnings and educational objectives of the WE BEAT program. Training sessions will include role-playing to enhance interventionists' competence in managing group dynamics and delivering interventions via telemedicine platforms. Ongoing fidelity will be monitored via live observation of 20% of sessions facilitated by each interventionist using fidelity checklists to assess adherence to the protocol, quality of delivery, and participant engagement. Observations and checklists will be completed by study chair and other trained interventionists. Regular supervision meetings will be conducted to provide feedback to each interventionist based on session reviews, helping them refine their delivery techniques.

WE BEAT Program Survey. To ensure participant receipt fidelity, an evaluative measure of the WE BEAT program will be completed at the final session (Week 5). This structured approach aims to maintain high fidelity across all elements of the intervention, thereby bolstering the internal validity and overall effectiveness of the program. Treatment fidelity findings will be reported as study findings, consistent with NIH BCC guidelines.

6.2 Medications/Treatments Permitted and Not Permitted during the Study

All participants in this study will receive UC as prescribed at each institution at which the study is being conducted. Participants will be treated with medications and other treatments at the discretion of their healthcare providers.

6.3 Procedures for Monitoring Participant Adherence

The interventionists will record session attendance. Adherence to the WE BEAT telemedicine group program will be defined as 70% overall (all participants), which is consistent with resilience intervention literature,[80] while maintaining 60% to delineate within-participant adherence (3 of 5 sessions). The within-participant outcome (**Section 2.1.4** Hypothesis 2) is supported by research demonstrating that even a single-session intervention can result in improved outcomes for adolescents with psychiatric concerns,[81] as well as increased growth-mindset among teens completing a single session promotive mental health intervention.[82,83,84] Additionally, 60% adherence for within-participant analysis was determined with our pragmatic trial design in mind, particularly because we know adolescents are busy and this population may experience illness/hospitalizations impacting session attendance.

Resources for Missed Sessions. While it will be encouraged, perfect adherence is not expected nor practical for this target population. As such, the WE BEAT intervention was designed to include 1) review of previous session in each session, 2) a look ahead to the next session in each session, and 3) an accompanying workbook that includes each skill/rationale for self-directed instruction and practice. Participants who miss a group session will be able to review the missed module in the applicable workbook section at their convenience. The post-session notification will serve as a reminder to review the missed material and allow participants to access videos and other resources that were shared in the missed group session.

6.4 Study Completion

Participants will be considered to have completed the study when they have completed the Week 30 assessment.

Participants in the UC arm will be offered an opportunity to participate in an open label WE BEAT telemedicine group program delivered by our study intervention core. Additional compensation or surveys will not be administered. This will be offered to support study recruitment and is aligned with the protocol's overall objective to provide increased access to psychosocial care to those with CHD. Participants in the intervention arm will not be offered post-study intervention.

Any additional mental health services for intervention arm and UC arm participants will be directed by his/her primary cardiology team. Participants may be contacted in the future for follow-up and about future studies.

7. SAFETY ASSESSMENTS AND MONITORING

7.1 Recording and Reporting Adverse Events

A major component of safety monitoring is ascertainment and reporting of adverse events, including adverse reactions to study intervention and/or questionnaires. The approach to these activities for this study is summarized in the sections that follow.

7.1.1 Definition of Adverse Events

An adverse event (AE) is any untoward medical occurrence experienced by a study participant. An event can be any unfavorable and unintended sign, symptom, laboratory abnormality, or disease associated with study participation.

Due to the nature of the study intervention, we do not anticipate that serious adverse events related to this study will occur. The minor potential risks to study participation are described in detail in **Section 11**, Ethics and Human Subjects Protection. Reportable events are limited to those associated with risks identified in **Section 11**, as well as active suicidal ideation and/or intent.

7.1.2 Classification of Adverse Events

Monitoring AEs requires that they be classified as to seriousness, severity, expectedness, and causality (potential relationship to the study intervention or questionnaires), all of which drive the reporting process.

a. Seriousness

A serious adverse event (SAE) is one that:

- Results in death,
- Is life-threatening (the participant was, in the view of the Principal Investigator (PI), in immediate danger of death from the event as it occurred),
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
- Is a congenital anomaly/birth defect in the offspring of a participant, or
- Is an Important Medical Event that may jeopardize the participant or may require medical/surgical intervention to prevent one of the serious adverse event outcomes.

b. Severity

The Common Terminology Criteria for Adverse Events (CTCAE) (http://ctep.cancer.gov), which incorporates elements of MedDRA terminology, provides a grading system that is used to categorize the severity of adverse events, as follows:

Grade 1	Mild	transient, requires no special treatment or intervention, does not interfere with daily activities
Grade 2	Moderate	alleviated with simple treatments, may limit daily activities
Grade 3	Severe	requires therapeutic intervention and interrupts daily activities
Grade 4	Life-threatening Or disabling	urgent or emergent intervention needed
Grade 5	Death	

c. Expectedness

The purpose of reporting is to provide new, important information on serious reactions or events previously unobserved or undocumented. Therefore, all AEs will be evaluated as to whether their occurrence was unexpected, using the following definitions:

- *Unexpected*: An unexpected AE or adverse reaction is one for which the nature or severity is not consistent with information in the protocol or consent form. An AE or adverse reaction also may be categorized as unexpected if the event has not previously been observed at the same specificity and/or severity.
- *Expected*: An event is considered expected if it is known to be associated with the disease state.

d. Causality

Causality assessment is required to determine which events require expedited reporting. The following criteria will be used to determine causality:

- *Not Related*: The event is clearly related to other factors, such as the participant's clinical state, or non-study drugs or interventions.
- *Possibly Related*: The event follows a compatible temporal sequence from the time of study evaluation but could have been produced by other factors such as the participant's clinical state or non-study drugs or interventions.
- *Probably Related*: The event follows a reasonable temporal sequence from the time of study evaluation and cannot be reasonably explained by other factors such as the participant's clinical state, or non-study drugs or interventions.

The seriousness, severity, expectedness, and causality of each event will be categorized and reported according to the reporting procedures in **Section 7.1.4**.

7.1.3 Identification of and Data Collection Procedures for AEs

AEs will be identified when they are reported to the clinical center or study interventionist during scheduled study visits/sessions. AEs will be assessed using self-report, physical examination data, and medical record review.

7.1.4 Reporting Timeframe and Procedures

Table 3. Reporting Timeframe of Adverse Events

Seriousness	Reporting Timeframe to the DCC
Fatal or life-threatening	Within 24 hours of learning of the event
Serious, but not fatal or life threatening	Within 24 hours of learning of the event
All other AEs	Within 7 calendar days of learning of the event

All SAEs are to be reported to the DCC within 24 hours of first knowledge of the event.

- *Fatal or life-threatening SAEs* that are *unexpected* and considered *possibly or probably related* to study participation will be reported by the DCC to the Medical Monitor (MM), NHLBI, and the PHN Data and Safety Monitoring Board (DSMB), as needed, within 7 calendar days after first knowledge of the event, followed by a complete report within 15 calendar days.
- *Serious (but not fatal or life-threatening) AEs* that are *unexpected* and considered *possibly or probably related* to study participation will be reported by the DCC to the MM, NHLBI, and PHN DSMB, as needed, within 15 calendar days after first knowledge of the event.

- All other *SAEs* that are *unrelated* to study participation will be reported semiannually to the DSMB and NHLBI.

All other AEs not meeting the criteria for expedited reporting will be reported to the DCC within 7 calendar days of first knowledge of the event. The DCC will report these AEs semiannually to the DSMB and NHLBI.

7.1.5 Reporting Adverse Events to IRBs for NIH-Supported Trials

The DCC is responsible for reporting adverse events (or facilitating site reports) to the sIRB according to sIRB guidelines. In addition to following sIRB reporting requirements, the site PI or designee is responsible for reporting all serious adverse events to the local IRB in accordance with local policies and procedures.

7.1.6 Follow-up of Participants after Adverse Events

For AEs with a causal relationship to study participation, follow-up by the PI is required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator.

7.2 Safety Monitoring

The Data and Safety Monitoring Plan for this trial will follow standard PHN monitoring principles. Oversight of data and safety is provided by the DSMB, appointed by NHLBI. The DSMB meets at least twice a year to review data on AEs, patient-reported outcomes, data quality, and study recruitment at regular intervals, and makes recommendations about study conduct to the NHLBI.

After each DSMB meeting, a summary report will be prepared within 30 days and will be distributed by NHLBI staff to the DCC for sIRB submission and review. Once obtained, sIRB approval of DSMB summaries will be disseminated to the trial investigators and coordinators, who will then forward the approval/summary report to their local IRB, as needed. The summary report will contain the following information:

- A statement that a DSMB review of outcome data, adverse events, and information relating to study performance across all centers took place on a given date.
- A statement as to whether or not the frequency of adverse events exceeded what was expected and indicated in the informed consent.
- A statement that a review of recent literature relevant to the research took place.
- The DSMB's recommendation with respect to progress or need for modification of the protocol or informed consent. If the DSMB recommends changes to the protocols or informed consent, the rationale for such changes and any relevant data will be provided.
- A statement that if safety concerns are identified, the NHLBI Program Official will communicate these promptly to the investigators.

In addition to the DSMB, a single IRB (sIRB) with reliance from local IRBs will also be responsible for the safe conduct of research at each study site. Participation in the study cannot begin at a clinical center until the sIRB (and local IRBs via reliance agreements) have approved the protocol. Per NHLBI policy, the consent form, if modified by individual sites, will be reviewed again centrally to ensure that no changes inconsistent with the Office of Human Research Protections policy of study design have occurred.

The DSMB and NHLBI are assisted by the MM in reviewing serious adverse events in PHN studies. The PHN MM is NHLBI's designee for determining causality and expectedness of all SAEs.

8. STATISTICS

8.1 Planned Statistical Analyses

This section briefly describes key aspects of the planned statistical analyses. A separate, detailed Statistical Analysis Plan (SAP) will be completed prior to database lock and unblinding of the data. Refer to **Section 2** for aims and their associated hypotheses and outcomes.

8.1.1 Primary Aim, Hypothesis 1, Primary Outcome

Primary Analysis of Primary Aim's Primary Outcome
Difference in CD-RISC© score (change score) from baseline to Week 5 (immediately post-intervention) will be calculated and compared between intervention and control arms. Intention-to-treat analysis will be used as the primary analysis.

The treatment arm difference in the mean change scores (i.e. change in CD-RISC© score from baseline to Week 5) will be assessed with an analysis of covariance (ANCOVA) with fixed factors for treatment arm with a continuous covariate of baseline CD-RISC© score.[85]

Secondary Analysis of Primary Aim's Primary Outcome
A similar analysis will be performed for the subpopulation of participants with moderate to low baseline resistance scores (**Section 8.8**).

8.1.2 Primary Aim, Hypothesis 1, Secondary Outcomes

Secondary outcomes for the primary aim are continuous measures and will be analyzed in the manner described above for the primary outcome. If measures are highly skewed, then regression modeling will be conducted on a suitably transformed outcome, where possible, to achieve a distribution that is closer to normality.

8.1.3 Primary Aim, Hypothesis 1A

The primary and secondary outcomes for Hypothesis 1A are the same as those described for Hypothesis 1 above (CD-RISC© change score and change in participant self-reported survey measures), but across different time periods—from baseline to Week 18 (3 months post-intervention) and baseline to Week 30 (6 months post-intervention). For both timepoints, the analysis outlined in **Section 8.1.1** will be used to compare intervention and control arms.

8.1.4 Primary Aim, Hypothesis 1B

The primary outcome for Hypothesis 1B is the CD-RISC© change score from baseline to Weeks 18 and 30, respectively, but instead of comparing the two treatment arms, the comparison will be between the two intervention-arm subpopulations: those randomized to the intervention with the booster session vs. those randomized to the intervention without the booster session. At both timepoints, the analysis outlined in **Section 8.1.1** will be used to compare the intervention-arm subpopulations. Additional sensitivity and secondary analyses will be described in the SAP.

8.1.5 Primary Aim, Hypothesis 2

Descriptive statistics will be provided to characterize adherence (primary outcome) and program satisfaction ratings (secondary outcome).

8.1.6 Primary Aim, Hypothesis 3

The primary and secondary outcomes for Hypothesis 3 mirror those described for Hypothesis 1 (CD-RISC© change score and change in participant self-reported survey measures). Regression modeling (bi-variate and multi-variate) of the change scores with family, social, and community-related covariates will be used to assess associations between the change scores and these predictors.

8.1.7 Secondary Aim 1

Appropriate regression modeling (bi-variate and multi-variate) of the key cardiac outcomes listed in Secondary Aim 1 Hypothesis 1 (**Section 2.2**) will be used to assess associations between the cardiac outcomes and key participant-reported predictors.

8.1.8 Secondary Aim 2

Regression modeling of change scores in key PRO outcomes (resilience score, etc.) will be used to assess associations with various biomarkers.

8.2 Sample Size and Power

The planned sample size for the study is N=390 enrolled participants (N=300 in the intervention arm and N=90 in the control arm). The sample size calculations (summarized in ***Table 4***) reflect the intention to power two secondary outcomes in addition to the primary outcome (see **Sections 8.2.1** - **8.2.2** below).

Based on prior studies, we conservatively estimated a cumulative dropout rate of 30% from baseline to Week 18 (post-intervention booster session). Specifically, dropout estimates will be assumed to be 15% for primary outcomes/endpoint (Week 5) and 18% for secondary outcomes/endpoint (Week 18). Our estimated dropout rates were informed by our WE BEAT pilot study (13% dropout rate)[35] and previous resilience interventions in ACHD, pediatric cancer, and pediatric diabetes, which have experienced dropout rates ranging 14-25%.[86,87,88]

Table 4: Summary of Sample Size Calculations

85% power for Primary Outcome
80% power for Booster vs No-Booster exploratory outcome
Based on assuming Commutative Dropout of 30% (with 15% at the 1st stage and 18% at the 2nd stage)

	Treatment	Control	Total
N in Treatment arm post-booster	83 x 2=166		
N in Treatment arm post-intervention after inflating for 18% drop-out	202		
N for Primary outcome	202	62	
N at baseline after inflating for 15% drop-out	238	73	311
Inflating for Stratification			
N at baseline after 20% inflation for stratification	298	91	389
Final N after rounding	300	90	390

8.2.1 Primary Outcome (Hypothesis 1)

Primary Analysis
A sample size of N=311 (238 participants in the intervention arm and 73 participants in the control arm) will provide 85% power to detect a mean treatment group difference in change from baseline to Week 5 in CD-RISC© score of 8.2%; that is, an improvement of 2.3 in the intervention arm compared to zero change in the control arm, assuming a Type I error of 0.05 and standard deviation of 5.25. A difference of 2.3, equivalent to an 8.2% increase from a baseline of 27.8, represents approximately 0.4 standard deviations and is considered clinically significant in this field.[36]

Assumptions used in power calculations:

- Primary Outcome – Change score defined as change in CD-RISC© score between baseline and Week 5
- Population – Age between 12 and 17 (< 18) years at baseline, moderate or severe CHD
- Comparison – Change score between 2 treatment groups (intervention vs. control)
- Baseline mean value of CD-RISC© score: 27.8±7.2 (based on historical data for a similar population)
- Standard deviation of the change score: 5.25 (based on historical data for a similar population)
- Dropout & incomplete testing: cumulative attrition (from enrollment to Week 18/post-booster) of 30%, including 15% attrition at the first stage (from baseline to Week 5/post-intervention; based on historical data for a similar population and conservatively inflated).
- $\alpha = .05$

Secondary Analysis (Hypothesis 1 for subpopulation with moderate-low baseline CD-RISC© score)
Under the same assumptions, an overall sample size of 389 (298 participants in the intervention arm and 91 participants in the control arm) will provide 85% power to detect treatment arm difference in change scores in a subset of 80% of participants after excluding those with the top 20% CD-RISC© scores at baseline.

8.2.2 Exploratory Secondary Outcome (Hypothesis 1B, booster session)

A sample size of N=202 in the intervention arm (equally divided between the booster and no-booster subpopulation) will provide 80% power to detect a mean treatment group difference in change from Week 5 to Week 18 in CD-RISC© score of 2.3 in the booster subpopulation compared to zero change in the no-booster subpopulation, assuming a Type I error of 0.05 and standard deviation of 5.25. A difference of 2.3 represents approximately 0.4 standard deviations.

Assumptions used in power calculations for the exploratory booster outcome:

- Since the booster session is a novel concept in this population, there is no historical data to inform our assumptions. Hence, we will rely on and replicate the assumptions used for the primary outcome, which were based on historical data
- Exploratory outcome – Change score defined as change in CD-RISC© score between baseline and Week 18 (immediately post-booster)
- Comparison – Change score between the two intervention arm subpopulations (booster vs. no-booster)
- Dropout & incomplete testing: cumulative attrition (from baseline to Week 18/post-booster) of 30%, including 18% attrition at the second stage (from Week 5/post-intervention to Week 18/post-booster)
- Standard deviation of the change score: 5.25 (used for the primary outcome)
- $\alpha = .05$.

Connection with calculations in **Section 8.2.1**:

- To power the primary outcome comparison between intervention and control arms at 85% with N=202 participants in the intervention arm, an additional N=62 participants in the control arm would be needed.
- Adjusting these numbers for a 15% attrition rate from baseline to Week 5 leads to N=311 (238 participants in the intervention arm and 73 participants in the control arm) at baseline.

8.3 Level of Significance

The type I error probability for the trial will be 0.05. Formal hypothesis testing will be performed only for the primary efficacy endpoint (**Section 8.1.1**). Thus, no adjustment for multiple comparisons will be necessary. No adjustments will be made for the multiple hypothesis tests among the secondary endpoints, but conclusions will be interpreted with caution due to the multiple tests proposed. The report will note the number of comparisons made, and the possibility that when many outcomes are analyzed, it is not unexpected that one or more might have a statistically significant treatment difference just by chance.

8.4 Interim Analyses and Stopping Rules for Termination of the Study

The study will be monitored by the PHN DSMB as described in **Section 7**. In addition to routine DSMB reviews, the following assessments and interim analysis will be performed at designated timepoints.

8.4.1 Reassessment of Assumptions

<u>High Resilience Group Cut-off Value Recalculation</u>
After baseline CD-RISC© is obtained for approximately 30% of the target sample size (N=~117 participants), the cut-off value for the high resilience group (defined as the top 20% of CD-RISC© scores) will be reevaluated. The updated cut-off value will be used for stratification (**Section 4.2.4**) for the remainder of the trial.

<u>Lumped Variance Recalculation</u>
After Week 5 CD-RISC© (primary outcome data) is obtained for approximately 30% of the target sample size (N=~117 participants), the variance of the primary outcome will be estimated, using a blinded method with lumped variance. If this estimated variance is higher than the one used for the sample size calculations (**Section 8.2**), then the sample size will be recalculated and may be increased correspondingly. Otherwise, the sample size will not change (i.e. a potential decrease of the sample size is not planned) and the trial will proceed as planned. This approach is based on blinded re-estimation of nuisance parameters and does not lead to inflation of type I error.[89] This is consistent with FDA guidance for industry in adaptive design of clinical trials.[90]

<u>Dropout Rate Reassessment</u>
After Week 18 CD-RISC© is obtained for approximately 30% of the target sample size (N=~117 participants), aggregate dropout rates will be reassessed. The sample size will be recalculated based on the observed dropout rates and may be adjusted accordingly after consultations with the DSMB.

8.4.2 Stopping Rules

An early evaluation of the treatment effect will be implemented for the interim analysis when approximately 50% of the target sample size (N=~195, unless sample size will be increased based on the lumped variance recalculation) have CD-RISC© score values at the Week 5 timepoint.

A non-binding recommendation of early stopping for efficacy, or conversion to a one-arm study, will be suggested to the DSMB if the estimate of the treatment effect obtained at the interim analysis is

positive and the corresponding one-sided p-value is lower than the reference value of alpha=0.0015. This reference value corresponds to the value of the O'Brien-Fleming spending function at the information fraction of 0.5.[89]

Interim analysis for futility will be performed via a conditional power analysis (with a 10% margin). Formal stopping boundaries are not proposed for other endpoints.

Based on the results of the primary analysis (immediately post-intervention), the DSMB may recommend stopping further follow-up (e.g. in case of a weak or absent efficacy signal).

8.4.3 Additional Considerations

DSMB Role
The DSMB may recommend stopping the study for other reasons, taking into account the efficacy and safety data from this trial and other studies, or concerns about study conduct. Early stopping rules are only guidelines; the DSMB may take a more global view of the trial during data monitoring.

Other Factors
Premature termination of this study may occur due to a regulatory authority decision, the impact of results released from other studies, failure to enroll, withdrawal of sIRB approval, or investigational intervention safety problems. In addition, NHLBI retains the right to discontinue the study prior to the inclusion of the intended number of participants but intends to exercise these rights only for valid scientific or administrative reasons.

8.5 Spurious Data Procedures

Consistency checks and range checks will be built into the data management system. This will allow many errors to be identified and corrected at the time of data entry. Queries regarding any problems with data will be sent to site coordinators regularly throughout the course of the study. Sites will also be monitored during the study. Therefore, spurious data are expected to be rare. Any data which are judged to be definitely incorrect, and which cannot be resolved, will be set to missing.

The study report will indicate the number of participants who have missing data on each study endpoint. For covariate-adjusted analyses, the number of participants who have missing data on the covariates will be reported. Imputation of missing data is not planned for this study.

Throughout the study, the rate, timing, and reasons for participant withdrawal will be monitored by site and treatment arm. Any site with a pattern of differential withdrawal by treatment arm will be queried. If necessary, retraining will take place or the site may be barred from enrolling additional participants to the study.

8.6 Deviation Reporting Procedure

Any modifications or deviations from the statistical plan described in this protocol will be documented in a revised SAP document.

8.7 Participants to be Included in Analyses

All randomized participants will be included in the analysis. Unless otherwise specified, all analyses will be intention-to-treat, i.e., participants will be analyzed in the group to which they were randomized.

Additionally, randomized participants will be compared with those who were eligible but not consented using available key baseline characteristics.

8.8 Subpopulations

The effect of the proposed intervention, if any, may vary according to participant subpopulation. Though formal testing is not planned, treatment effect (intervention vs. control) will be examined in the prespecified subpopulations in secondary analyses. Subpopulations are defined based on characteristics known at the time of randomization and have two strata. These strata are defined prospectively as:

- Age at enrollment (12-14 vs. 15-17)
- Lesion complexity (moderate, severe)
- Baseline resilience (high vs. moderate/low)
- Baseline depression (per PROMIS, y/n)
- Baseline anxiety (per PROMIS, y/n)
- Baseline mental health condition (y/n, per reported diagnosis)
- Baseline mental health treatment (y/n, per reported diagnosis)

A 95% confidence interval of the difference in treatment group means for the primary outcome will be provided within each subpopulation.

Additionally, treatment group differences for the primary efficacy endpoint will be analyzed using the approach described in **Section 8.1.1** in the subpopulation of participants with moderate/low baseline resilience score (approximately 80% of enrolled participants). Of note, due to stratification (**Section 4.2.4**), participants were randomized into this subpopulation, and the study was designed to provide 85% of power in this subpopulation.

9. DATA MANAGEMENT

An Electronic Data Capture (EDC) system will be used for the study that is designed to support reliable and secure data entry for clinical research purposes. The system also provides seamless integration of eCRFs and paper-based CRFs within a single protocol if desired; implementation of protocol amendments; and SAS and XML study data exports.

One EDC system that may be utilized for this study is a customizable, complete end-to-end solution for collecting data from participants via their smartphones or any device connected to the internet via the MyDataHelps app (available on iOS, Android, and web browser). Participants join the study database via the app, which enables them to consent and enroll into the study, fill out study surveys, receive engagement notifications and reminders, dispense biospecimen collection kits, and track obtained biospecimens sent to the biorepository. There is also an optional feature to share data from various sensors and wearable technologies (e.g., fitness trackers, continuous glucose monitors, blood pressure cuffs, etc.).

9.1 Data Entry

Data will be entered directly by participants and study staff via a fully validated and Title 21 of the Code of Federal Regulations (CFR) Part 11-compliant, secure web application.

9.2 Data Validation and Monitoring

Integrated into the data entry system are real time validations, including both inter- and intra-instrument data checks. Inconsistent or questionable values are flagged during entry, and an edit report is automatically generated to the data entry client. These edit reports provide the information necessary to investigate any data entry errors or resolved questions regarding out-of-range or questionable values.

9.3 Data Security and Integrity

Data is securely stored in the HIPAA compliant, Meaningful Use Certified EDC HIEBus platform, and is then exported in an easy-to-use format. The MyDataHelps platform complies with the security and privacy controls defined by NIST 800-53 Rev. 5 at the FISMA Moderate and Privacy baseline. They regularly undergo external formal assessments by a FedRAMP-accredited Third Party Assessment Organization (3PAO). The platform has been granted an Authorization to Operate (ATO) by the National Institutes of Health (NIH) and is FDA Part 11 Compliant.

All data changes are written to an audit trail. The audit trail identifies the data item by table, column and key field. The entry includes the user, date and time, as well as the old value and new value. Both participant-related data as well as trial configuration data are written to the audit trail. Data are saved at regular intervals during data entry to prevent loss of information in the event of a disruption of the Internet connection. In the unlikely event of a major disruption, a backup connection allows full access to the data management system.

Several levels of security are employed to ensure privacy and integrity of the study data, including the following: Study access requires use of assigned usernames and passwords. Individual roles and access levels are assigned by the study data manager. Passwords are changed regularly. Web-based entry uses secure socket layer data encryption. Data will not be stored on laptop computers.

9.4 Biospecimen Tracking

Specimen tracking will begin from the time that the biospecimen is obtained for shipment via at-home collection kits or the time of receipt at the site, during shipment to and handling at the PHN Biorepository, and through shipment to other core laboratories, as applicable. Each specimen will be labeled with a bar-coded label identified by a unique specimen number that is different from the participant's unique study ID number. The master list linking the barcode numbers to the participant study ID numbers will be maintained under password protection in the data management system at the DCC. This blinding code system will maintain the confidentiality of the specimens yet allowing linkage of the specimens with clinical study data for analyses.

10. QUALITY CONTROL AND QUALITY ASSURANCE

The DCC has primary responsibility for QC/QA activities of the phenotypic data. The DCC also requires that the sites complete certain QC activities, most of which are monitored by the DCC and study chair. The key QC/QA activities are:

- Development of a study manual;
- Carefully constructed data collection forms/CRFs accompanied by manuals of instruction;
- Sign-off procedures for applicable CRFs;
- Central protocol training and certification of all site data collection staff with the use of standardized checklists;
- Data management training and certification of site personnel completing data entry and/or data management;
- Verification of participant eligibility;
- Fidelity checks on intervention sites;
- On-going monitoring of all protocols/data collection activities; and,
- Completion of reliability and/or pilot studies for key measurements as appropriate.

11. ETHICS AND HUMAN SUBJECTS CONSIDERATIONS

11.1 Potential Risks

The overall risks of participation in this study are no more than minimal. Potential risks include:

a) breach of confidentiality due to telemedicine group participation and/or collection of personally identifying information,
b) discomfort/distress when answering survey questions or during group intervention, and
c) minor discomfort associated with blood draws.

<u>Confidentiality (due to group participation)</u>
While the sharing of personal contact information will not be encouraged through the telemedicine group program, it is possible that participants will voluntarily share such information in an effort to maintain relationships and peer support. These peer connections are no more than minimally likely to pose additional risks and are similar to risks experienced through school and community settings but must be acknowledged for the purposes of this study.

<u>Psychological Discomfort/Distress</u>
In the previous WE BEAT pilot study experience, no safety/risk concerns presented among intervention participants during group sessions requiring follow-up. However, it is possible that participation in this study could cause psychological distress or lead to identification of mental health concern requiring a higher level of care, or identification of child protective services concern resulting in mandated reporting. Although these may cause stress or strain on participants, these possible

events would occur within the context of supporting participants (i.e., not causing additional harms). In summary, the potential risks of this study are minimal. The alternative to participating in the protocol is simply non-participation.

We estimate low risk of emotional discomfort and/or distress completing study measures/surveys. There is no evidence across the broad scientific literature to suggest that assessing depressive symptoms or mental health concerns prompts risks related to mood/behavior, however, we will still engage in actions to protect against such distress. Specifically, participants (and participating parents) will be reminded that they do not have to answer any survey questions that they prefer not to answer or those that may cause distressing feelings.

Biospecimen Collection
Minor temporary discomfort may be associated with the removal of blood by venipuncture. There is a risk of bruising, and a very small amount of bleeding associated with blood drawing. There is also a very small risk of infection at the site. Whenever possible, blood samples will be gathered when the participant is scheduled for routine blood testing or procedures. There are no known risks to collecting saliva, hair, or urine.

11.2 Confidentiality, Protection against Risks

Investigators will take all reasonable measures to protect the confidentiality of participants and their families, including the following:

Use of Study ID numbers
Each participant is assigned a study identification number (SID). All interview and clinical research data are stripped of identifiers and labeled with the study number. Any enrollment logs with participant identifiers will be maintained at each site in a secured, locked location available only to site study staff. Samples for the biorepository will be labeled with sample ID numbers and not the SID. The informed consent form states that study data will be made available to the Data Coordinating Center (DCC) and NIH/NHLBI to ensure study safety and quality control. The participant's name and any other identifying information will not appear in any presentation or publication resulting from this study.

Global Unique Identifiers (where applicable)
A unique identification number, called a Global Unique Identifier or GUID, will be assigned to each study participant, if applicable. A GUID is a universal ID that allows researchers to share data specific to a study participant without exposing personally identifiable information (PII) and at the same time be able to match participants across labs, databases or research studies. Personal information does not leave the research site, only a unique set of encrypted codes that are then decrypted to determine if the participant already exists within the data repository. The GUID is then sent to the enrolling site. This tokenization process is similar to the one used by the National Database for Autism Research. The GUID would allow data from this study to be combined with data from other research studies or databases in an effort to improve outcomes in children and young adults with heart disease.

Intervention-associated Discomfort/Distress
During WE BEAT group sessions, interventionists will iterate that participant comfort is a priority of intervention delivery, and they may participate (on screen, off screen, muted, chat text) in a manner that feels most comfortable. WE BEAT interventionists will all be licensed psychologists, and as such, will have considerable expertise in the mitigation of emotional discomfort and/or distress. Interventionists will undergo training specific to responding to risks and concerns that may present in the group telemedicine sessions.

If a participant expresses discomfort, distress, or a need for additional mental health support during or after group sessions, the interventionist will complete an assessment and conduct safety planning as needed. Safety planning may include:

- contacting a parent/guardian to disclose safety/risk concerns if imminent risk is identified,
- contacting psychosocial clinician at participant's PHN site for additional follow-up to occur locally, and/or
- providing general information on how to identify and obtain additional local mental health referrals, including provision of the national mental health crisis line (988).

Information from clinical studies or medical records may be placed into a central data repository in the future, such as the National Center for Biotechnology Information (NCBI) repository. Data and samples will be de-identified before submission to this or any other central repository.

11.3 Potential Benefits

Treatment and Study Findings

In the WE BEAT pilot trial, participants experienced positive psychological wellbeing effects from the intervention. Similar benefits may be experienced by those in the intervention arm, as well as those in the usual care arm who opt to participate in an open-label WE BEAT program following their study completion. Participation in the study may lead to increased knowledge about the benefits of psychological health for those with CHD and subsequent increased openness to future resources or support.

Biospecimens

Currently, there is no known direct benefit from the participation of the participant and family in the biorepository. However, we hope that DNA and serum donation will help investigators to learn more about the relationship between genetic factors or biomarkers and longer-term cardiac and neurodevelopmental outcomes. This information may help physicians provide better answers to families' questions regarding causes, risk, and recurrence risks. It may also provide clues to future interventions and/or treatments.

Indirect Benefit

There might be an indirect benefit from the awareness that study results may help to improve the care of children with similar problems in the future. Families may derive a sense of altruism, accomplishment, and contribution to furthering understanding of the problem through their participation.

11.4 Risk/Benefit Ratio and Importance of Information to Be Obtained

The risk/benefit ratio is favorable for this study and adverse events are not anticipated. The baseline risk is minimal because the intervention is a well-being and resiliency-building virtual program. In addition, although an individual participant may not benefit from participation, the results of this study will make important contributions to the improvement of knowledge about CHD, the management of complex CHD in adolescents, and ultimately in the improvement of treatment and prognosis for affected families.

12. STUDY LIMITATIONS

Study limitations include:

1. **Generalizability.** Lack of intervention availability in languages other than English or Spanish limits generalizability of intervention and study results to other patient populations.
2. **Recruitment, Retention and Program Management.** Intervention studies present unique study management challenges. It is likely that participants will have variable availability. Finding consistent meeting times across 5 weeks for a group of participants will be challenging and may limit recruitment, participation and retention. We will attempt to mitigate this limitation by offering intervention groups across diverse days and times with interventionists across time zones.
3. **Standardization.** Maintaining consistency in intervention delivery can be difficult in virtual settings. Variations in interventionists' styles or technical issues can affect the uniformity of the intervention. We will attempt to mitigate this limitation by keeping to a small core team of interventionists, ensuring robust interventionist training with use of a manualized intervention manual and fidelity monitoring planning, and continued access to interventionist training/development as needed.
4. **Engagement and Interaction.** Virtual settings may limit opportunities for natural interactions and non-verbal communication, which are important aspects of group dynamics and psychoeducation. Some participants may be comfortable with telemedicine-based, group sessions. The pilot study experience suggests many young people are comfortable with using the chat features. We will reiterate to participants that their comfort is our priority, and they may participate in a manner that feels most comfortable to them.
5. **Statistical Power.** The study may be underpowered for subpopulation analyses and some secondary endpoints.

13. REFERENCES

[1] Whitney DG, Peterson MD. US national and state-level prevalence of mental health disorders and disparities of mental health care use in children. JAMA pediatrics. 2019;173(4):389-391.

[2] Racine N, McArthur BA, Cooke JE, Eirich R, Zhu J, Madigan S. Global prevalence of depressive and anxiety symptoms in children and adolescents during COVID-19: a meta-analysis. JAMA pediatrics. 2021;175(11):1142-1150.

[3] Gonzalez VJ, Kimbro RT, Cutitta KE, et al. Mental health disorders in children with congenital heart disease. Pediatrics. 2021;147(2).

[4] DeMaso DR, Calderon J, Taylor GA, et al. Psychiatric disorders in adolescents with single ventricle congenital heart disease. Pediatrics. 2017;139(3).

[5] McCormick AD, Wilde MM, Charpie CE, et al. Psychological functioning in paediatric patients with single ventricle heart disease: a systematic review. Cardiology in the Young. 2022;32(2):173-184.

[6] Kovacs AH, Saidi AS, Kuhl EA, et al. Depression and anxiety in adult congenital heart disease: Predictors and prevalence. International Journal of Cardiology. 2009;137(2):158-164.

[7] Elgar FJ, Pförtner T-K, Moor I, De Clercq B, Stevens GW, Currie C. Socioeconomic inequalities in adolescent health 2002–2010: a time-series analysis of 34 countries participating in the Health Behaviour in School-aged Children study. *The Lancet*. 2015;385(9982):2088-2095.

[8] Gonzalez VJ, Kimbro RT, Shabosky JC, et al. Racial Disparities in Mental Health Disorders in Youth with Chronic Medical Conditions. The Journal of Pediatrics. 2023:113411.

[9] Kovacs AH, Brouillette J, Ibeziako P, et al. Psychological outcomes and interventions for individuals with congenital heart disease: a scientific statement from the American Heart Association. Circulation: Cardiovascular Quality and Outcomes. 2022;15(8):e000110.

[10] Cassidy AR, Butler SC, Briend J, et al. Neurodevelopmental and psychosocial interventions for individuals with CHD: a research agenda and recommendations from the Cardiac Neurodevelopmental Outcome Collaborative. Cardiology in the Young. 2021:1-12.

[11] Opotowsky AR, Allen KY, Bucholz EM, et al. Pediatric and Congenital Cardiovascular Disease Research Challenges and Opportunities: JACC Review Topic of the Week. Journal of the American College of Cardiology. 2022;80(23):2239-2250.

[12] Psychological interventions for people affected by childhood-onset heart disease: A systematic review [press release]. US: American Psychological Association. 2019.

[13] Cousino MK, Pasquali SK, Romano JC, et al. Impact of the COVID-19 pandemic on CHD care and emotional wellbeing. Cardiology in the Young. 2021;31(5):822-828.

[14] Levine GN, Cohen BE, Commodore-Mensah Y, et al. Psychological health, well-being, and the mind-heart-body connection: a scientific statement from the American Heart Association. Circulation. 2021;143(10):e763-e783. Carazo MR, Kolodziej MS, DeWitt ES, et al. Prevalence and Prognostic Association of a Clinical Diagnosis of Depression in Adult Congenital Heart Disease: Results of the Boston Adult Congenital Heart Disease Biobank. Journal of the American Heart Association. 2020;9(9):e014820.

[15] Carazo MR, Kolodziej MS, DeWitt ES, et al. Prevalence and Prognostic Association of a Clinical Diagnosis of Depression in Adult Congenital Heart Disease: Results of the Boston Adult Congenital Heart Disease Biobank. Journal of the American Heart Association. 2020;9(9):e014820.

[16] Ko JM, Tecson KM, Al Rashida V, et al. Clinical and psychological drivers of perceived health status in adults with congenital heart disease. The American Journal of Cardiology. 2018;121(3):377-381.

[17] McCabe N, Dunbar SB, Butler J, Higgins M, Book W, Reilly C. Antecedents of self-care in adults with congenital heart defects. International journal of cardiology. 2015;201:610-615.

[18] Woolf-King SE, Anger A, Arnold EA, Weiss SJ, Teitel D. Mental health among parents of children with critical congenital heart defects: a systematic review. Journal of the American Heart Association. 2017;6(2):e004862.

[19] Sood E, Lisanti AJ, Woolf-King SE, et al. Parent mental health and family functioning following diagnosis of CHD: A research agenda and recommendations from the Cardiac Neurodevelopmental Outcome Collaborative. Cardiology in the Young. 2021;31(6):900-914.

[20] Ludomirsky AB, Bucholz EM, Newburger JW. Association of Financial Hardship Because of Medical Bills With Adverse Outcomes Among Families of Children With Congenital Heart Disease. JAMA Cardiol. 2021;6(6):713-717.

[21] Rosenberg AR, Yi-Frazier JP. Commentary: Resilience Defined: An Alternative Perspective. Journal of Pediatric Psychology. 2016;41(5):506-509.

[22] Kichler JC, Kaugars AS. Topical Review: Applying Positive Development Principles to Group Interventions for the Promotion of Family Resilience in Pediatric Psychology. Journal of Pediatric Psychology. 2015;40(9):978-980.

[23] Masten AS. 113C6Resilience in Developmental Systems: Principles, Pathways, and Protective Processes in Research and Practice. In: Ungar M, ed. Multisystemic Resilience: Adaptation and Transformation in Contexts of Change: Oxford University Press; 2021:0.

[24] Ungar M, Theron L. Resilience and mental health: How multisystemic processes contribute to positive outcomes. The Lancet Psychiatry. 2020;7(5):441-448.

[25] Glenn T, Cousino MK, Wernovsky G, Schuchardt EL. Resilient Hearts: Measuring Resiliency in Young People With Congenital Heart Disease. Journal of the American Heart Association. 2023:e029847.

[26] Rosenberg AR, Bradford MC, McCauley E, et al. Promoting resilience in adolescents and young adults with cancer: Results from the PRISM randomized controlled trial. Cancer. 2018;124(19):3909-3917.

[27] Yi-Frazier JP, Yaptangco M, Semana S, et al. The association of personal resilience with stress, coping, and diabetes outcomes in adolescents with type 1 diabetes: Variable-and person-focused approaches. Journal of Health Psychology. 2015;20(9):1196-1206.

[28] Moon JR, Huh J, Kang I-S, Park SW, June T-G, Lee HJ. Relationship between depression and resilience in adolescents with congenital heart disease. Am Heart Assoc; 2006.

[29] Luberto CM, Wang A, Li R, Pagliaro J, Park ER, Bhatt A. Videoconference-delivered Mind-Body Resiliency Training in Adults with congenital heart disease: A pilot feasibility trial. International Journal of Cardiology Congenital Heart Disease. 2022;7:100324.

[30] Kovacs AH, Grace SL, Kentner AC, Nolan RP, Silversides CK, Irvine MJ. Feasibility and outcomes in a pilot randomized controlled trial of a psychosocial intervention for adults with congenital heart disease. Canadian Journal of Cardiology. 2018;34(6):766-773.

[31] Olsson CA, Boyce MF, Toumbourou JW, Sawyer SM. The role of peer support in facilitating psychosocial adjustment to chronic illness in adolescence. Clinical Child Psychology and Psychiatry. 2005;10(1):78-87.

[32] Rosenberg AR, Yi-Frazier JP, Eaton L, et al. Promoting Resilience in Stress Management: A Pilot Study of a Novel Resilience-Promoting Intervention for Adolescents and Young Adults With Serious Illness. Journal of Pediatric Psychology. 2015;40(9):992-999.

[33] Cousino MK, Dusing CR, Rea KE, et al. Developing the WE BEAT Well-Being Education Programme to foster resilience and build connection in paediatric heart disease. Cardiology in the Young. 2024:1-7.

[34] Glenn T, Smith C, Miller VA, et al. From worries to resilience: a qualitative study of the psychosocial experiences of diverse adolescents and young adults with heart failure and their caregivers. Cardiology in the Young. 2024:1-8.

[35] Cousino MK, Rea KE, Dusing CR, Glenn T, Armstrong B, Yu S, Lowery R, Les AS, Goldberg CS, Hansen JE, Schumacher KR. A pilot study of the WE BEAT Well-Being Education Programme to build resilience in adolescents with heart disease. Cardiology in the Young. 2024:1-8.

[36] Mesman E, Vreeker A, Hillegers M. Resilience and mental health in children and adolescents: an update of the recent literature and future directions. Current Opinion in Psychiatry 34(6):p 586-592, November 2021. | DOI: 10.1097/YCO.0000000000000741.

[37] Ford I, Norrie J. Pragmatic trials. New England Journal of Medicine. 2016;375(5):454-463.

[38] Loudon K, Treweek S, Sullivan F, Donnan P, Thorpe KE, Zwarenstein M. The PRECIS-2 tool: designing trials that are fit for purpose. BMJ. 2015;350.

[39] Williford DN, McTate EA, Hood AM, et al. Psychologists as leaders in equitable science: Applications of antiracism and community participatory strategies in a pediatric behavioral medicine clinical trial. American Psychologist. 2023;78(2):107.

[40] Kilbourne AM, Switzer G, Hyman K, Crowley-Matoka M, Fine MJ. Advancing Health Disparities Research Within the Health Care System: A Conceptual Framework. American Journal of Public Health. 2006;96(12):2113-2121.

[41] Ellis DA, Rhind J, Carcone AI, et al. Optimizing recruitment of black adolescents into behavioral research: A multi-center study. Journal of pediatric psychology. 2021;46(6):611-620.

[42] Cui Z, Seburg EM, Sherwood NE, Faith MS, Ward DS. Recruitment and retention in obesity prevention and treatment trials targeting minority or low-income children: a review of the clinical trials registration database. Trials. 2015;16:1-15.

[43] Campbell-Sills L, Stein MB. Psychometric analysis and refinement of the connor–davidson resilience scale (CD-RISC): Validation of a 10-item measure of resilience. Journal of Traumatic Stress: Official Publication of The International Society for Traumatic Stress Studies. 2007;20(6):1019-1028.

[44] Connor KM, Davidson JR. Development of a new resilience scale: The Connor-Davidson resilience scale (CD-RISC). Depression and anxiety. 2003;18(2):76-82.

[45] Yu X-n, Lau JT, Mak WW, Zhang J, Lui WW. Factor structure and psychometric properties of the Connor-Davidson Resilience Scale among Chinese adolescents. Comprehensive Psychiatry. 2011;52(2):218-224.

[46] Levey EJ, Rondon MB, Sanchez S, Williams MA, Gelaye B. Psychometric properties of the Spanish version of the 10-item Connor Davidson Resilience Scale© (CD-RISC©) among adolescent mothers in Peru. Journal of Child & Adolescent Trauma. 2021;14:29-40.

[47] Irwin DE, Stucky BD, Thissen D, et al. Sampling plan and patient characteristics of the PROMIS® pediatrics large-scale survey. Quality of Life Research. 2010;19:585-594.

[48] DeWalt DA, Gross HE, Gipson DS, et al. PROMIS® pediatric self-report scales distinguish subgroups of children within and across six common pediatric chronic health conditions. Quality of Life Research. 2015;24:2195-2208.

[49] Forrest CB, Bevans KB, Tucker C, et al. Commentary: the patient-reported outcome measurement information system (PROMIS®) for children and youth: application to pediatric psychology. Journal of Pediatric Psychology. 2012;37(6):614-621.

[50] Kessler RC, Andrews G, Colpe LJ, et al. Short screening scales to monitor population prevalences and trends in non-specific psychological distress. Psychological Medicine. 2002;32(6):959-976.

[51] Mewton L, Kessler RC, Slade T, et al. The psychometric properties of the Kessler Psychological Distress Scale (K6) in a general population sample of adolescents. Psychological assessment. 2016;28(10):1232.

[52] Varni JW, Seid M, Kurtin PS. PedsQL™ 4.0: Reliability and validity of the Pediatric Quality of Life Inventory™ Version 4.0 Generic Core Scales in healthy and patient populations. Medical care. 2001:800-812.

[53] Uzark K, Jones K, Burwinkle TM, Varni JW. The Pediatric Quality of Life Inventory™ in children with heart disease. Progress in pediatric cardiology. 2003;18(2):141-149.

[54] González-Gil T, Mendoza-Soto A, Alonso-Lloret F, Castro-Murga R, Pose-Becerra C, Martín-Arribas MC. The Spanish version of the health-related quality of life questionnaire for children and adolescents with heart disease (PedsQL™). Revista Española de Cardiologia (English Edition). 2012;65(3):249-257.

[55] Mellion K, Uzark K, Cassedy A, et al. Health-related quality of life outcomes in children and adolescents with congenital heart disease. Journal of Pediatrics. 2014;164(4):781-788. e781.

[56] Marino BS, Uzark K, Ittenbach R, Drotar D. Evaluation of quality of life in children with heart disease. Progress in Pediatric Cardiology. 2010;29(2):131-138.

[57] Lloyd-Jones DM, Allen NB, Anderson CA, Black T, Brewer LC, Foraker RE, Grandner MA, Lavretsky H, Perak AM, Sharma G, Rosamond W. Life's essential 8: updating and enhancing the American Heart Association's construct of cardiovascular health: a presidential advisory from the American Heart Association. Circulation. 2022 Aug 2;146(5):e18-43

[58] Hummel K, Whittaker S, Sillett N, Basken A, Berghammer M, Chalela T, Chauhan J, Garcia LA, Hasan B, Jenkins K, Ladak LA. Development of an international standard set of clinical and patient-reported outcomes for children and adults with congenital heart disease: a report from the International Consortium for Health Outcomes Measurement Congenital Heart Disease Working Group. European Heart Journal-Quality of Care and Clinical Outcomes. 2021 Oct 1;7(4):354-65.

[59] Zimet GD, Dahlem NW, Zimet SG, Farley GK. The Multidimensional Scale of Perceived Social Support. Journal of Personality Assessment 1988;52:30-41.

[60] Multidimensional-Scale-of-Perceived-Social-Support-Spanish.pdf

[61] Bruwer B, Emsley R, Kidd M, Lochner C, Seedat S. Psychometric properties of the Multidimensional Scale of Perceived Social Support in youth. Compr Psychiatry. 2008 Mar-Apr;49(2):195-201. doi: 10.1016/j.comppsych.2007.09.002. Epub 2007 Dec 21. PMID: 18243894.

[62] Canty-Mitchell J, Zimet GD. Psychometric properties of the Multidimensional Scale of Perceived Social Support in urban adolescents. Am J Community Psychol. 2000 Jun;28(3):391-400. doi: 10.1023/A:1005109522457. PMID: 10945123.

[63] Moons P, Van Deyk K, De Geest S, Gewillig M, Budts W. Is the severity of congenital heart disease associated with the quality of life and perceived health of adult patients? Heart. 2005;91(9):1193-1198.

[64] Fergus S, Zimmerman MA. Adolescent resilience: A framework for understanding healthy development in the face of risk. Annu Rev Public Health. 2005;26:399-419.

[65] Steiner JM, Blakeney EA-R, Baden AC, et al. Definitions of resilience and resilience resource use as described by adults with congenital heart disease. International Journal of Cardiology Congenital Heart Disease. 2023;12:100447.

[66] Joyce S, Shand F, Tighe J, Laurent SJ, Bryant RA, Harvey SB. Road to resilience: a systematic review and meta-analysis of resilience training programmes and interventions. BMJ open. 2018;8(6):e017858.

[67] Rosenberg AR, Wolfe J, Bradford MC, et al. Resilience and psychosocial outcomes in parents of children with cancer. Pediatric blood & cancer. 2014;61(3):552-557.

[68] Lewis P, Klineberg E, Towns S, Moore K, Steinbeck K. The effects of introducing peer support to young people with a chronic illness. Journal of Child and Family Studies. 2016;25:2541-2553.

[69] Levine GN, Lange RA, Bairey-Merz CN, et al. Meditation and cardiovascular risk reduction: a scientific statement from the American Heart Association. Journal of the American Heart Association. 2017;6(10):e002218.

[70] Meiklejohn J, Phillips C, Freedman ML, et al. Integrating mindfulness training into K-12 education: Fostering the resilience of teachers and students. Mindfulness. 2012;3:291-307.

[71] Pidgeon AM, Keye M. Relationship between resilience, mindfulness, and pyschological well-being in University students. International Journal of Liberal Arts and Social Science. 2014;2(5):27-32.

[72] Cohen R, Bavishi C, Rozanski A. Purpose in life and its relationship to all-cause mortality and cardiovascular events: A meta-analysis. Psychosomatic medicine. 2016;78(2):122-133.

[73] Law E, Fisher E, Eccleston C, Palermo TM. Psychological interventions for parents of children and adolescents with chronic illness. Cochrane Database of Systematic Reviews. 2019(3).

[74] Mak WW, Ng IS, Wong CC. Resilience: enhancing well-being through the positive cognitive triad. Journal of counseling psychology. 2011;58(4):610.

[75] Huffman JC, Beale EE, Celano CM, et al. Effects of optimism and gratitude on physical activity, biomarkers, and readmissions after an acute coronary syndrome: the gratitude research in acute coronary events study. Circulation: Cardiovascular Quality and Outcomes. 2016;9(1):55-63.

[76] Cousin L, Redwine L, Bricker C, Kip K, Buck H. Effect of gratitude on cardiovascular health outcomes: a state-of-the-science review. The Journal of Positive Psychology. 2021;16(3):348-355.

[77] Legler SR, Beale EE, Celano CM, Beach SR, Healy BC, Huffman JC. State gratitude for one's life and health after an acute coronary syndrome: Prospective associations with physical activity, medical adherence and re-hospitalizations. The journal of positive psychology. 2019;14(3):283-291.

[78] Vieselmeyer J, Holguin J, Mezulis A. The role of resilience and gratitude in posttraumatic stress and growth following a campus shooting. Psychological Trauma: Theory, Research, Practice, and Policy. 2017;9(1):62.

[79] Bellg AJ, Borrelli B, Resnick B, Hecht J, Minicucci DS, Ory M, Ogedegbe G, Orwig D, Ernst D, Czajkowski S. Enhancing treatment fidelity in health behavior change studies: best practices and recommendations from the NIH Behavior Change Consortium. Health psychology. 2004 Sep;23(5):443.

[80] Steiner, J.M., Marshall, A.R., Kovacs, A.H., Engelberg, R.A., Brumback, L., Stout, K.K., Longenecker, C.T., Joyce, P. and Rosenberg, A.R., 2024. Rationale and design of a randomized controlled clinical trial of a resilience-building intervention in adults with congenital heart disease. Contemporary Clinical Trials, 145, p.107638.

[81] Schleider JL, Weisz JR. Little Treatments, Promising Effects? Meta-Analysis of Single-Session Interventions for Youth Psychiatric Problems. J Am Acad Child Adolesc Psychiatry. 2017 Feb;56(2):107-115. doi: 10.1016/j.jaac.2016.11.007. Epub 2016 Nov 25. PMID: 28117056.

[82] Schleider JL, Weisz JR. Reducing risk for anxiety and depression in adolescents: Effects of a single-session intervention teaching that personality can change. Behav Res Ther. 2016 Dec;87:170-181. doi: 10.1016/j.brat.2016.09.011. Epub 2016 Sep 26. PMID: 27697671; PMCID: PMC5127737.

[83] Schleider JL, Weisz JR. A single-session growth mindset intervention for adolescent anxiety and depression: 9-month outcomes of a randomized trial. J Child Psychol Psychiatry. 2018 Feb;59(2):160-170. doi: 10.1111/jcpp.12811. Epub 2017 Sep 18. PMID: 28921523.

[84] Schleider JL, Burnette JL, Widman L, Hoyt C, Prinstein MJ. Randomized Trial of a Single-Session Growth Mind-Set Intervention for Rural Adolescents' Internalizing and Externalizing Problems. J Clin Child Adolesc Psychol. 2020 Sep-Oct;49(5):660-672. doi: 10.1080/15374416.2019.1622123. Epub 2019 Jun 20. PMID: 31219698; PMCID: PMC6923626.

[85] Senn S., Julious S. Measurement in clinical trils: a neglected issue for statisticians. Statistics in Medicine. 2009, 28:3189-3209.

[86] Kovacs AH, Grace SL, Kentner AC, Nolan RP, Silversides CK, Irvine MJ. Feasibility and Outcomes in a Pilot Randomized Controlled Trial of a Psychosocial Intervention for Adults With Congenital Heart Disease. Can J Cardiol. 2018 Jun;34(6):766-773. doi: 10.1016/j.cjca.2018.02.023. Epub 2018 Mar 2. PMID: 29801741.

[87] Rosenberg, A.R., Bradford, M.C., McCauley, E., Curtis, J.R., Wolfe, J., Baker, K.S. and Yi-Frazier, J.P. (2018), Promoting resilience in adolescents and young adults with cancer: Results from the PRISM randomized controlled trial. Cancer, 124: 3909-3917. https://doi.org/10.1002/cncr.31666

[88] O'Donnell MB, Scott SR, Ellisor BM, Cao VT, Zhou C, Bradford MC, Pihoker C, DeSalvo DJ, Malik FS, Hilliard ME, Rosenberg AR, Yi-Frazier JP. Protocol for the Promoting Resilience in Stress Management (PRISM) intervention: A multi-site randomized controlled trial for adolescents with type 1 diabetes. Contemp Clin Trials. 2023 Jan;124:107017. doi: 10.1016/j.cct.2022.107017. Epub 2022 Nov 21. PMID: 36410689; PMCID: PMC9839528.

[89] Proshan M, Lan G, WIttes J. Statistical monitoring of clinical trials. Springer. 2007.

[90] Adaptive Design Clinical Trials for Drugs and Biologics, Guidance for Industry.