

RESEARCH ARTICLE

Virtual reality cognitive intervention for heart failure: CORE study protocol

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Abstract

Introduction: Heart failure (HF) is a prevalent, serious chronic illness that affects 6.5 million adults in the United States. Among patients with HF, the prevalence of attention impairment is reported to range from 15% to 27%. Although attention is fundamental to human activities including HF self-care, cognitive interventions for patients with HF that target improvement in attention are scarce. The COgnitive intervention to Restore attention using nature Environment (CORE) study aims to test the preliminary efficacy of the newly developed Nature-VR, a virtual reality-based cognitive intervention that is based on the restorative effects of nature. Nature-VR development was guided by Attention Restoration Theory. The target outcomes are attention, HF self-care, and health-related quality of life (HRQoL). Our exploratory aims examine the associations between attention and several putative/established HF biomarkers (eg, oxygen saturation, brain-derived neurotrophic factor, apolipoprotein E, dopamine receptor, and dopamine transporter genes) as well as the effect of Nature-VR on cognitive performance in other domains (ie, global cognition, memory, visuospatial, executive function, and language), cardiac and neurological events, and mortality.

Methods: This single-blinded, two-group randomized-controlled pilot study will enroll 74 participants with HF. The Nature-VR intervention group will view three-dimensional nature pictures using a virtual reality headset for 10 minutes per day, 5 days per week for 4 weeks (a total of 200 minutes). The active comparison group, Urban-VR, will view three-dimensional urban pictures using a virtual reality headset to match the Nature-VR intervention in intervention dose and delivery mode, but not

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in content. After baseline interviews, four follow-up interviews will be conducted to assess sustained effects of Nature-VR at 4, 8, 26, and 52 weeks.

Discussion: The importance and novelty of this study consists of using a first-of-its kind, immersive virtual reality technology to target attention and in investigating the health outcomes of the Nature-VR cognitive intervention among patients with HF.

KEYWORDS

apolipoprotein E, attention, augmented reality, biomarkers, brain-derived neurotrophic factor, clinical trial protocol, cognition, dopamine receptor, dopamine transporter, genomics, heart failure, virtual reality

1 | BACKGROUND

Heart failure (HF) is a prevalent, serious chronic illness affecting 6.5 million American adults.¹ The prevalence of this disease is projected to increase by 46% by 2030.¹ A major issue for patients with HF is cognitive dysfunction, which has a prevalence of 24% to 80%.²⁻⁴ The most likely etiology of cognitive dysfunction in HF is inadequate cerebral blood flow.^{2,3,5} In addition to memory, attention is one of the most commonly impaired cognitive domains in HF.⁶⁻⁸ Attention is critical in supporting effective human activities, and thus poor attention function is often associated with inadequate HF self-care (eg, lack of adherence to a low sodium diet, non-adherence to medication, and poor symptom management).⁹⁻¹¹ As shown in past studies, inadequate HF self-care is associated with higher mortality and hospitalizations and diminished health-related quality of life (HRQoL).^{12,13} Given that attention is fundamental to learning and maintaining HF self-care, the development of interventions aiming to improve attention among patients with HF is warranted.

Approaches to developing interventions to improve attention in HF need to be guided by theory because theory provides fundamental understanding of the problem that interventions target.¹⁴ One relevant theory is Attention Restoration Theory, which proposes that attention can be restored and improved by interacting with nature.^{15,16} Studies guided by this theory have shown that natural restorative environment (Nature) interventions can improve attention in diverse populations. For example, engaging in nature-related activities (eg, walking in the park, gardening) improved attention among breast cancer survivors,¹⁷ and viewing nature pictures on computer screens improved attention among healthy adults.^{18,19} In our pilot study consisting of a randomized controlled crossover design, a computer-based Nature intervention using two-dimensional pictures of nature was tested for its efficacy compared to a computer-based active comparison intervention of two-dimensional urban pictures among 20 participants with HF and 20 age-matched healthy adults. The results indicated that participants with HF had poorer attention and showed small to near-medium effects of the Nature intervention on improving attention.²⁰

Newer virtual reality (VR) technology can now create three-dimensional environments to better simulate the natural environment and provide a more immersive experience than two-dimensional

computer-based pictures.^{21,22} Thus to extend our pilot study, our study team developed a prototype of a VR-based nature intervention (Nature-VR) using three-dimensional pictures delivered by a VR headset and tested its feasibility among 10 participants with HF. This feasibility study examined study completion, safety, satisfaction, and attention improvement with the Nature-VR prototype among these 10 participants with HF.²³ The intervention was delivered by laptop computer for five participants with HF and by VR for five participants with HF. Attention was examined immediately pre- and post-intervention. All 10 participants completed the study, and no adverse events were reported during or immediately after the interventions. Participants who received the intervention by the VR mode were slightly more satisfied. Participants in the computer-based Nature intervention were provided an opportunity to try Nature-VR at the end of the interview, with four of five participants trying and preferring Nature-VR.²³ With regard to attention improvement, performance on tests of attention was consistently better after Nature-VR compared with the computer-based Nature intervention, except for the Digit Span Forward test.²³ Effect sizes were calculated using Hedge's *gs*. Changes in measures were modeled using a linear model with a single term for group (Nature-VR and computer-based Nature intervention). Ninety-five percent confidence intervals for the effect size were estimated by generating 2000 bootstrap samples and refitting the model to each bootstrap sample. Large effect sizes were found for attention measured with Multi-Source Interference Task (faster response time [Hedge's *gs* = -1.620] and higher accuracy [Hedge's *gs* = 1.262] on the congruent trials) and Trail Making Test A (faster response time [Hedge's *gs* = -1.205]) (Figure 1).

Building upon the feasibility study with the prototype the Nature-VR intervention and the active comparison condition (Urban-VR) have now been developed. The purpose of this study is to test the preliminary efficacy of this latest version of Nature-VR on attention, HF self-care, and HRQoL using a two-group single-blinded randomized controlled design.

2 | METHODS

The COgnitive intervention to Restore attention using nature Environment (CORE) study was approved by the Indiana University

institutional review board. The study protocol is registered on ClinicalTrials.gov (NCT 04485507). Because the coronavirus disease 2019 (COVID-19) pandemic has necessitated some changes to the original protocol, both the original study protocol and the modifications made in response to the pandemic are presented. In the interest of participant and researcher safety, the COVID protocol will be used until the pandemic subsides.

2.1 | Study design

The proposed study is a two-group single-blinded randomized controlled pilot study. Participants with HF will have five data collection interviews (Figure 2). Primary and secondary outcomes will be examined at baseline, immediately post-intervention (4 weeks), 8, 26 and 52 weeks (1 year). Follow-up data will provide information about intervention effects over time.

2.2 | Specific aims and hypotheses

The primary aim is to evaluate the preliminary efficacy of Nature-VR on attention among participants with HF. The secondary aims are to evaluate the preliminary efficacy of Nature-VR on the secondary outcomes of HF self-care and HRQoL. The study will test the following hypotheses:

Hypothesis 1: Compared with participants receiving the active comparison condition (Urban-VR), participants receiving Nature-VR intervention will have greater improvement in attention over time (at 4, 8, 26, and 52 weeks).

Hypothesis 2a: Compared with participants receiving the active comparison condition (Urban-VR), participants receiving Nature-VR intervention will have greater improvement in HF self-care over time (at 4, 8, 26, and 52 weeks).

Hypothesis 2b: Compared with participants receiving the active comparison condition (Urban-VR), participants receiving Nature-VR intervention will have greater improvement in HRQoL over time (at 4, 8, 26, and 52 weeks).

Exploratory aim 1 will examine associations between attention and putative/established HF biomarkers (ie, oxygen saturation,^{6,24} serum brain-derived neurotrophic factor [BDNF],^{20,25} and four genetic biomarkers—the BDNF,^{26,27} apolipoprotein E [APOE],^{28,29} dopamine receptor, and dopamine transporter^{30,31} genes).

Exploratory aim 2 will examine the preliminary efficacy of Nature-VR on other cognitive domains (ie, global cognition, memory, executive function, and language), cardiac events (ie, hospitalizations, emergency department visits), neurological events (ie, diagnosis of cognitive impairment, such as mild cognitive impairment, dementia), and mortality.

RESEARCH IN CONTEXT

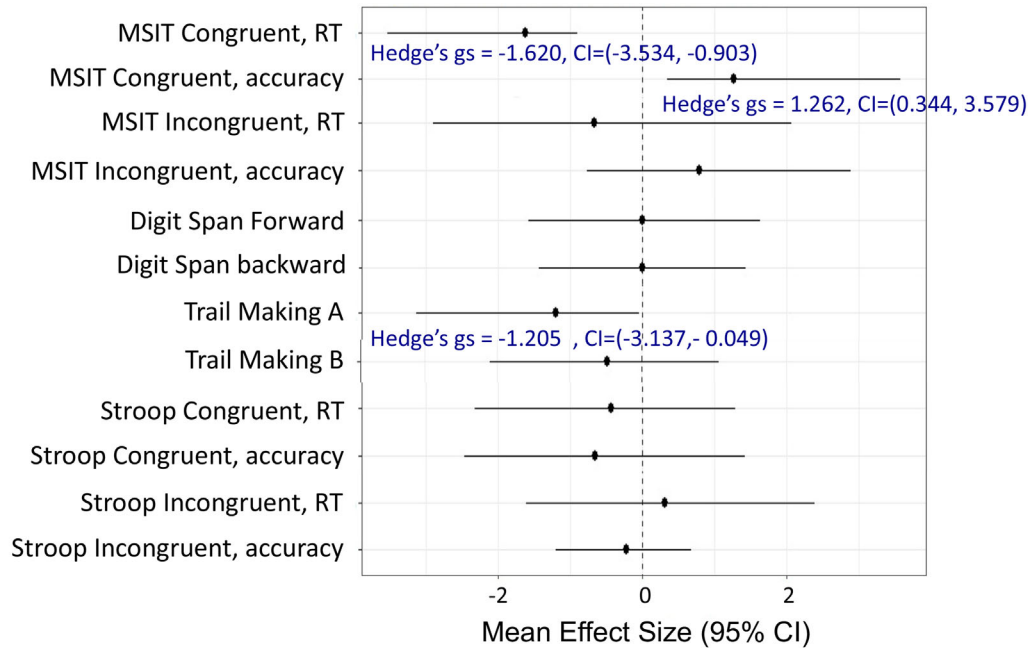
- 1. Systematic review:** To identify the relevant literature, the authors searched PubMed using combinations of relevant keywords (ie, chronic heart failure [HF], cognitive training/intervention, virtual and augmented reality). No studies were found of virtual reality-based cognitive interventions to improve attention or other cognitive function in HF. Studies of cognitive training/intervention in HF have been appropriately cited.
- 2. Interpretation:** New, theory-based interventions are needed to improve attention among patients with HF. This study assesses preliminary efficacy of a new virtual reality intervention using a library of 360° nature photographs for improving attention, HF self-care, and health-related quality of life (HRQoL) in HF.
- 3. Future directions:** (1) Populations with chronic conditions, including HF, that are vulnerable to cognitive impairment need targeted interventions to improve cognitive function; (2) easy, enjoyable, cost-effective interventions need to be developed and tested; and (3) intervention responders and non-responders need to be characterized by examining the relationship between intervention responsiveness and patient characteristics and relevant biomarkers.

HIGHLIGHTS

- Nature-VR is a theory-based virtual reality cognitive intervention
- We describe the framework and methodology of Nature-VR cognitive intervention study
- We will test if Nature-VR improves attention and health-related outcomes.

2.3 | Sample

We will enroll 74 participants (37 in each group) to retain 30 in each group by the end of the study (projecting a 19% attrition rate). This sample size was calculated based on our previous studies.^{23,32} For the primary outcome of attention, the effect sizes of the computer-based nature intervention compared to those of the computer-based urban comparison condition among 20 participants with HF ranged from 0.02 to 0.45 (Cohen's *d*).³² Given that the Hedge's *g*s effect sizes of the three-dimensional Nature-VR prototype was larger compared to the computer-based two-dimensional nature intervention in our feasibility study (Figure 1),²³ a medium effect size was used in this sample



Notes. CI = 95% confidence interval, ES = effect size measured by Hedge's g_s , RT = response time.

FIGURE 1 Hedge's g_s effect sizes of changes on attention after Nature-VR prototype compared to the computer-based Nature intervention ($n = 10$)

justification. Our power analyses indicate that with a sample size of 60 (30 participants per group) we will have 84% power to detect the preliminary efficacy of the Nature-VR intervention for improving attention compared to the Urban-VR comparison condition among participants with HF.

Given the lack of intervention studies testing the efficacy of the Nature-VR intervention on HF self-care and HRQoL, our sample size calculation is based on guidelines for pilot studies.^{33,34} A sample size of 30 for each group should allow us to estimate the effect sizes that can be used to calculate the sample sizes of future efficacy studies.

Participants will be recruited from the Indiana University Health (IUH) outpatient cardiology clinics. Inclusion criteria are (1) adults (>21 years); (2) diagnosed with chronic HF Stage C as defined by Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, and Japanese Heart Failure Society; and (3) able to communicate in English. Exclusion criteria are (1) uncorrected visual impairment; (2) major neurological disease (eg, Alzheimer's disease, Parkinson disease, etc.); and (3) major psychiatric disease (eg, schizophrenia, bipolar disease, etc.).

2.4 | Procedures

Written informed consent will be obtained from all participants prior to enrollment. The interviews will be conducted at either the participant's home or our research office at Indiana University School of Nursing. Our single blinded methodology requires us to use a separate intervention and data collection research assistants (RAs). The inter-

vention RA will collect participants' demographic and clinical characteristics and conduct the baseline interviews. After baseline interview, the RA will randomize the participant. 1:1 randomization will be generated using SAS statistical software by the team biostatistician. The randomization results will be concealed from the principal investigator (PI) and the data collection RA. The participants will be told not to share their group assignment with the data collection RA and the PI during their follow-up interviews. The two RAs will be instructed to not communicate with each other about randomization. The intervention RA will instruct participants on how to complete the activities for either Nature-VR or Urban-VR with the written intervention manual. During the 4-week intervention phase, participants in each group will receive weekly phone calls to check if they have experienced technical issues with the VR headset and to answer questions. After the intervention phase, the data collection RA who will remain blinded to group assignment will meet participants for four follow-up interviews. Attention and secondary outcomes will be evaluated immediately after completion of the intervention (4 weeks visit) as well as at 8, 26, and 52 weeks. During each study time point, oxygen saturation will be monitored. A pulse oximetry (eg, Nonin WristOx2) will be placed on the participants' index finger of the non-dominant hand. Peripheral blood for genetic biomarkers (*APOE*, *BDNF*, *dopamine receptor*, and *dopamine transporter genes*) will be collected by a phlebotomist at the outpatient cardiology clinic or by our study team member who is an RN at baseline. Peripheral blood for serum BDNF will be collected at baseline and at 4 weeks. Collected blood samples will be transferred to the Indiana Clinical and Translational Sciences Institute (CTSI) Storage Facility and analyzed at Indiana Biobank.

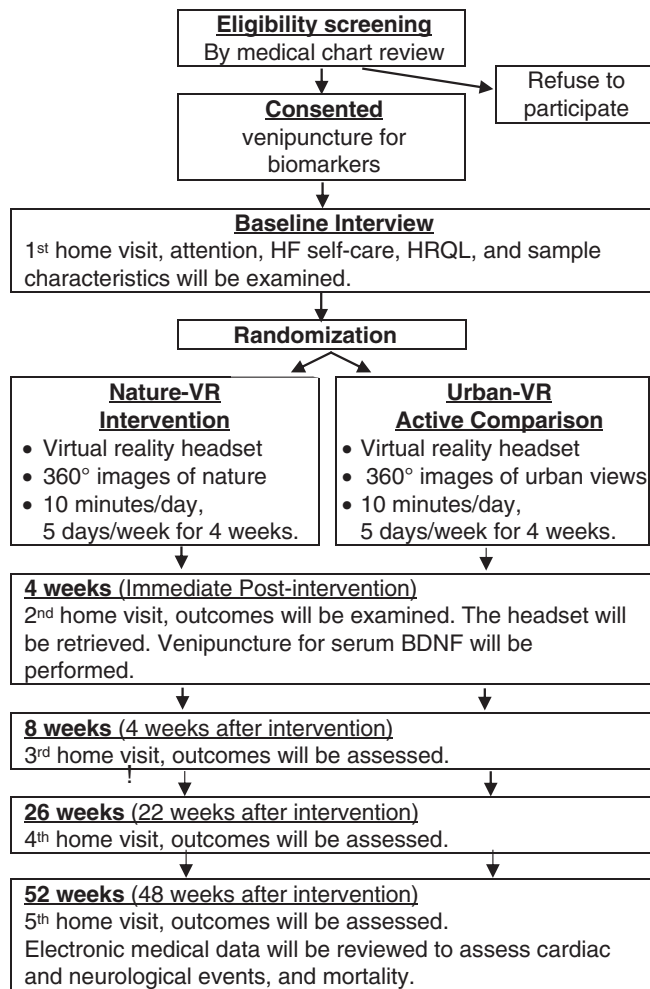


FIGURE 2 Research design and procedure

2.5 | Intervention and active comparison condition

The intervention and active comparison condition were developed by the PI with consultation from the Advanced Visualization Lab at Indiana University to use VR technology. The development was guided by the Attention Restoration Theory, and all contents in both Nature-VR and Urban-VR were validated in consistency with the four qualities of the restorative environment as explained below in the Content section.

2.5.1 | Nature-VR intervention

Participants will receive a VR headset and will be asked to perform the intervention 10 minutes per day, 5 days per week over 4 weeks, for a total of 200 minutes (= 3.3 hours). This *intervention dose* was chosen based on four factors. First, young adults can sustain attention for 10 to 20 minutes before needing reinforcement to maintain their focus.^{35,36} Because attention span may decrease with aging,³⁷ attention interventions likely need to be brief for efficacy without fatigue. Second, a meta-analysis of interventions using nature activities suggested that 5-minute interventions are optimal for improving

self-esteem and mood.³⁸ Third, in our preliminary study participants had interventions of ~7 minutes, which led to small to medium effect sizes.³² Finally, participants with HF in our previous feasibility study were asked about the adequacy of the intervention dose and reported it to be adequate.²³ Thus 10 minutes per day was deemed appropriate for the Nature-VR intervention.

The 4-week *intervention duration* was selected based on two previous cognitive intervention studies. First, the ACTIVE study, a large cognitive training trial in 2832 healthy older adults, supports our rationale for 4 weeks of cognitive intervention.³⁹ Second, Cimprich tested a Nature intervention of 36 days to improve attention among 157 participants with breast cancer and found a medium effect.¹⁷

Content (library of nature pictures): According to Attention Restoration Theory, nature has four qualities that provide a favorable environment for restoring attention (ie, feelings of being away, soft fascination, extended feelings, and high compatibility).^{15,16} To ensure consistency with the theory, an intervention map was developed using the four qualities and the four nature domains (vegetation, sky, water, and earth).¹⁵ This map was used to guide our choice of nature pictures. The pictures selected for Nature-VR were validated for consistency with the theory by three PhD-level nurse researchers. The final 200 nature images were grouped into 20 sets (10 photographs per set) (Figure 3).

Delivery mode: To view the photographs in the Nature-VR intervention participants will use the Oculus Go, a head-mounted goggle that displays 360° pictures (See Figure 3). The goggles are used to limit eye movement inside and to prevent visual distractions from outside the device. The Oculus application was developed by the Indiana University Advanced Visualization Lab to display three-dimensional photographs for the Nature-VR intervention. The application stores all 200 photographs, and automatically plays the 360° spherical photographs (1 minute per photograph) when the Oculus Go device is turned on and the application initiated. The application has a time-stamping function to monitor the time spent.

2.5.2 | Urban-VR active comparison condition

The active comparison condition was developed to resemble as closely as possible the Nature-VR intervention. Participants in the comparison condition will also receive a VR headset for research. They will be similarly instructed to perform the active comparison condition 10 minutes per day, 5 days per week over 4 weeks, for a total of 200 minutes (= 3.3 hours). The active comparison image library will consist of 360° pictures of an urban environment. The urban views (eg, a parking structure, traffic lights, indoor images of buildings) have fewer or less of the four qualities of attention restorative stimuli, according to guiding theory.^{15,16}

2.6 | Measures

Attention, our primary outcome, will be assessed using objective and subjective measures at baseline and at 4, 8, 26 and 52 weeks of



(A) Content of Nature-VR (This picture of a park was taken by Dr. Jung)
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(B) Virtual reality head-mount goggle as the delivery mode, Oculus Go
(source: www.oculus.com)

FIGURE 3 Examples of Nature-VR intervention

follow-up. The objective measures of attention to be used are the Multi-Source Interference Task, Digit Span, Trail Making, and Stroop tests (Table 1). Subjective attention—a patient-reported outcome—will also be examined using the Attentional Function Index.⁴⁰ This self-reported questionnaire consists of 13 items that assess perceived effectiveness of behaviors requiring attention on a visual analogue scale (0 to 10). Higher scores indicate better subjective attention.⁴⁰

HF self-care will be examined by the Self-Care of Heart Failure Index v7.2.⁴¹ This self-report questionnaire consists of 39 items. Higher scores indicate better self-care and scores ≥ 70 indicate adequate self-care.

HRQoL will be measured by the Minnesota Living with Heart Failure Questionnaire.^{42,43} This self-report questionnaire consists of 21 items that ask participants to rate how their HF condition has impacted their physical and emotional health. Lower scores indicate better HRQoL. This measure is predictive of mortality, and a 4.84-point change in the total score is clinically meaningful.⁴⁴

In addition to the attention measures described above we will use the Montreal Cognitive Assessment (MoCA) to measure global cognition, the Hopkins Verbal Learning Test (HVLT) and Craft Story to assess verbal memory, the Benson Figure Copy to assess visuospatial memory, Category Fluency to assess language, and Digit Symbol to assess executive function. Health events and mortality will be collected by reviewing electronic medical records (EMRs) and doing online searches for obituaries.

Demographic (ie, age, education, gender, socioeconomic status, handedness, body mass index, smoking history), and clinical (ie, ejection fraction, HF type and severity, B-type natriuretic peptide, medications, cardiac devices, depressive symptoms, comorbidity) characteristics will be collected at baseline and used as possible covariates.

Pulse oximetry will be used to monitor oxygen saturation at each study time point. Venipuncture for serum BDNF will be performed at baseline and 4 weeks. Venipuncture for genetic biomarkers (ie, *APOE*, *BDNF*, dopamine receptor, and dopamine transporter genes) will be performed at baseline.

2.7 | Statistical analysis plan

Distributions based on density plots will be examined for normality of the data and to detect outliers. If not normally distributed, non-parametric methods will be used. Baseline equivalencies between the groups will be evaluated using independent *t*-tests and chi-square tests. Observed scores of outcome variables at pre- and post-intervention will be presented for both groups. An intent-to-treat approach will be used to ensure that observed differences between groups are not attributable to differential dropout.⁴⁵ Analyses for each study aim will be performed using the statistical package SAS at an alpha of .05 or less.

TABLE 1 Measures of attention

Measures	Description	Reliability	Validity
Multi-Source Interference Task	This computerized test examines the cingulo-fronto-parietal cognitive/attention network. ^{52,53} In this task participants are asked to identify a target number that is different from two other numbers displayed on a computer screen. There are two types of trials: congruent and incongruent. For the congruent trials a target number is always matched by its position on a button (eg, 100, 020, or 223), whereas for incongruent trials the target number is never matched with its position on a button (eg, 010, 233, or 232). A faster response time and lower error rate indicates better attention. In this study, congruent trial scores will be used to assess sustained attention, and differences between congruent and incongruent trials will be used to assess directed attention.	Reliable activation of the dorsal anterior cingulate cortex and prefrontal cortex was found during the test in a meta-analysis of nine studies with healthy adults. ⁵⁴	Construct validity was confirmed among 22 patients with HF. ⁵⁵
Digit Span Test	This test measures attention, specifically, attention span. ⁵⁶ Participant are asked to repeat the sequence of numbers that they were told. The test has two parts, Forward, repeating the numbers in the same sequence, and Backward, repeating the numbers backwards from the last to the first number. The numbers of digits participants repeated correctly are scored. Higher scores indicate better attention.	Test-retest reliability coefficients ranged between .66 and .89. ⁵⁶	Construct validity was supported by comparing healthy and closed head injury patients. ⁵⁷
Trail Making Test	This test measures attention requiring visual tracking and task switching. ^{58,59} There are two parts: A and B. In Part A, participants are asked to connect a series of randomly arrayed circles numbered from 1 to 25 in order as quickly as possible. In Part B, participants are asked to connect a series of 25 circles numbered from 1 to 13 randomly intermixed with letters from A to L, alternating between numbers and letters in ascending order. The time to complete including the time for correction of any errors is recorded, called response time. A longer response time indicates poorer attention. In this study, Part A scores will be used to assess sustained attention and differences between Part A and B will be used to assess directed attention.	Test-retest reliability ranged from .86 to .96 in 20 patients with HF. ³²	Construct validity was supported among healthy adults and patients with closed head injury. ⁵⁷
Stroop Test	This test measures attention involving in selective processing of different visual features while ignoring distractions on the test (letters and ink colors of color words). ⁶⁰ A computerized Stroop test was programmed using E-Prime software. Participants are asked to read the letters or ink colors of four color words (ie, red, blue, yellow, and green) and press the designated keyboard on the laptop computer. There are two types of trials. In congruent trials, the color names have same letters and print colors (eg, red in red ink). In incongruent trials, the color names do not match to the print colors (eg, red in blue ink). There are two conditions: switching and non-switching. In switching conditions, the commands are switched from word to color, or color to word. In non-switching conditions, the commands are the same (color to color, or word to word). Differences in performance between switching and non-switching conditions will be used to assess attention switching. Congruent trial scores will be used to assess sustained attention and differences between congruent and incongruent trials will be used to assess directed attention.	Reliability was satisfactory. ^{61,62}	Construct validity was supported in patients with traumatic brain injury. ⁶³ Impaired performance on Stroop test was most common in patients with frontal lobe lesions in a meta-analysis. ⁶⁴

TABLE 2 Protocol changes responding to the COVID-19 pandemic

Study procedure	Changes in methods	Descriptions
Recruitment	Phone recruitment and verbal consent	Possibly eligible adults with HF will be contacted by phone. A copy of the informed consent and HIPAA form will be sent to possibly eligible participants via email or mail prior to the verbal consent and authorization. We will obtain verbal consent without a written signature on the consent form and HIPAA form after explaining our study procedures with our informed consent and HIPAA forms. Participants will be asked if they have any questions before they provide verbal consent to participate in the study.
Data collection	Phone interviews	To avoid physical contact, data will be collected by phone interviews instead of face-to-face interviews at baseline, 4, 8, 26, and 52 weeks. Our original protocol included two computerized (ie, Multi-Source Interference Task, Stroop Test) and two paper-pencil based cognitive tests (ie, Benson Figure Copy, Digit Symbol tests) that cannot be administered via phone. Thus, the Oral Trail Making (primary outcome measure) and Digit Span tests will be used to assess attention. A blind version of the MoCA will be used to assess global cognition. Verbal Fluency will be administered to examine executive function. In addition to Category Fluency, the Verbal Naming Test will be administered to examine language. The Hopkins Verbal Learning Test and Craft Story will be administered as planned to assess verbal memory. Oxygen saturation will not be monitored during the phone interviews.
	Saliva samples	Venipuncture was planned to measure serum BDNF levels and collect DNA for genetic biomarkers (ie, <i>BDNF Met</i> , <i>APOE ε4</i> , 7-repeat of dopamine receptor, and 10-repeat of dopamine transporter alleles). Due to the need to collect data remotely, saliva samples will instead be collected for genetic biomarkers using the OGR-600 saliva kit (DNA Genotek). The saliva sample collection kit will be delivered to the participants by the intervention RA with the intervention kit. The intervention RA will instruct how to collect saliva sample and ask to leave their samples outside their front doors for collection by the RA. The intervention RA will deliver the saliva sample to the storage facility on campus. Oxygen saturation and serum BDNF will not be collected in this modified study protocol.
Intervention delivery	Drop-off based remote option of delivery	A study team member will call participants to set up a time to drop off the intervention kit (virtual reality headset, intervention manual binder). The intervention kit will be dropped off outside the participant's front door after which the participant will be called to let them know the kit has been delivered. Instructions for how to use the intervention kit will be given in the follow up phone call. If a participant wants to receive the intervention in person, the intervention RA may give the intervention instructions to the participant outdoors in person. Throughout the entire process, adequate social distancing of 6 feet or more will be maintained. After the intervention phase, participants will be asked to leave the intervention kit outside their front door for a pick up at a pre-arranged date and time.

Abbreviations: APOE, apolipoprotein E; BDNF, brain-derived neurotrophic factor; DNA, deoxyribonucleic acid; HIPAA, Health Insurance Portability and Accountability Act; MoCA, Montreal Cognitive Assessment; RA, research assistant.

To test the effect of Nature-VR on attention (*hypothesis 1*), HF self-care, and HRQoL (*hypotheses 2a* and *2b*, respectively), we will use linear mixed models to model attention performance over time with group, time, and group by time interaction variables. Adherence to the intervention (ie, minutes spent using Nature-VR, which is objective evidence collected by using time-stamping function of the Oculus application in the device), HF severity, comorbidity, and gender will be tested as potential covariates. The mixed models will produce valid estimates for missing data at random.

We will employ three analytic strategies to demonstrate the relationships between attention and possible biomarkers. The relationships of baseline attention with oxygen saturation, BDNF serum levels over time, *BDNF Met*, *APOE ε4*, 7-repeat of *dopamine receptor* and 10-repeat of *dopamine transporter* alleles will be examined using analysis of covariance (ANCOVA) models, while adjusting for participants' ages. The changes in oxygen saturation and serum BDNF levels in relation to attention changes at 4-week follow-up will be examined using ANCOVA models adjusting for age. Those biomarkers that show

significant associations with attention will be added to models for *hypotheses 1, 2a*, and *2b* to examine different levels of responsiveness to the intervention based on the biomarkers.

We will assess the effect of Nature-VR on the other cognitive domains (*exploratory aim 2*) using linear mixed models similar to the analysis plan for *hypothesis 1, 2a*, and *2b*. Binomial logistic regressions will be used to test the preliminary efficacy of Nature-VR on cardiac and neurological events and mortality adjusting for covariates.

Effect sizes of Nature-VR will be examined by omega-squared for the interaction terms.⁴⁶ Ninety-five percent confidence intervals will be estimated using the non-parametric bootstrap method.

2.8 | Potential difficulties and alternative approaches

Although HF prevalence is similar for men and women,¹ women are underrepresented in HF research studies.⁴⁷ To address this issue we

will recruit equal numbers of women and men by monitoring monthly recruitment. If the enrollment of women is <50% for three consecutive months, we will modify the recruitment brochure to be more attractive to women (eg, more pictures of women) and identify more outpatient clinics for recruitment of women. Second, the African American population in the United States is 12.6%. To recruit a diverse sample, study invitations for African American will be prioritized during recruitment. Finally, using a VR headset may be challenging to some participants. To help participants with the use of this technology, written instructions and a phone helpline will be provided.

2.9 | Research conduct during the COVID-19 pandemic

The CORE study is being conducted during the worldwide pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease 2019 [COVID-19]). The COVID-19 pandemic has led to study protocol modifications to meet the COVID-19 restrictions for human research. Given that our study population is adults with HF who are identified as high risk for more serious symptoms of COVID-19, we are conducting the study with a remote option without direct physical contact with participants. Major changes are recruitment over the phone with verbal consent, data collection by phone interviews, saliva sample collection, and drop-off-based intervention delivery. Because of the remote option, necessary changes were made to measures. Detailed information is presented in Table 2. The modified study protocol using a remote data collection and intervention delivery has been approved by the university institutional review board.

3 | DISCUSSION

Participant enrollment was initiated in July 2020 to evaluate the preliminary efficacy of the Nature-VR intervention for improving attention, HF self-care, and HRQoL compared to the Urban-VR active comparison condition. In this new study, 74 participants with HF will be enrolled and followed up 52 weeks (1 year) after baseline.

The Nature-VR is theoretically sound and innovative. The incorporation of VR technology into this restorative cognitive intervention will provide immersive experiences by visually simulating a real natural environment. The use of this immersive technology is ideal for participants who have limited access to natural environments (eg, due to limited physical function, inclement weather, or urban living with limited access to green space) and less opportunity to engage with nature directly. VR technology is safe and may increase the strength of the intervention effect, as demonstrated by past studies, including our feasibility study.⁴⁸⁻⁵¹

Investigating the effects of Nature-VR on HF self-care and HRQoL will contribute to understanding the relationships between cognitive dysfunction and the health outcomes as well as provide another approach to improve HF management if efficacious. Previous studies have been more focused on educating patients to change self-care

behaviors. Cognitive interventions may support the patients' learning during the education, improve perception of the HF symptoms, and help make decisions on managing the symptoms.

The Nature-VR has great potential to improve attention and prevent attention impairment, and may lead to better self-care and HRQoL among patients with HF. The Nature-VR intervention can be delivered in patients' homes at low cost (eg, the Oculus Go, head-mounted goggles costs \$300). If findings are as hypothesized, the Nature-VR and Urban-VR interventions will be used to test full-scale efficacy of the Nature-VR intervention with a sample size powered from the effect sizes calculated from this study. If no effect is seen, this pilot study will contribute to the development of knowledge about attention changes over time in HF, future design of biobehavioral cognitive interventions, and development of possible biomarkers associated with attention.

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CONFLICT OF INTEREST

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