A Pilot Feasibility Testing of a Small Randomized Controlled Trial to Evaluate a Telemedicine Stress Management and Lifestyle Group Intervention for Patients with Symptomatic Chronic Hepatitis C

Study Protocol: Version 7.0, 16Nov2021

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STUDY PROTOCOL
DOCUMENT HISTORY

Document	Date of Issue	Summary
Original Version of Protocol, Version 1.0	22Sept2019	• First version of the protocol : 22Sept2019 • Submitted to UNC IRB: 22Sept2019 • Approved by IRB • Submitted to NINR
Version 2.0	07Feb2020	The following changes have been made: • Updated: o exclusion criteria o reimbursement procedures o randomization procedures o salivary cortisol procedures o research team information • Removed: o use of study website; replaced with a Google drive o use of Zoom; study will only utilize WebEx • Clarified research staff roles in study procedures
Version 3.0	20Mar2020	**During the COVID-19 outbreak, Wave 1 is allowed to forego saliva sample testing, if necessary, pending allowed research operations** Additionally, the following changes have been made: • Recruitment and consenting procedures clarified and updated to include verbal telephone consent • Changed randomization groups so that Group 1 will consist of 7 patients and Group 2 will consist of 9 patients; total number of participants remains the same (n=32) • Updated location of some study procedures to be conducted in a private area and for study documents to be stored in locked, secure area • Minor updates to IT's role and responsibility • Typographical and grammatical errors corrected throughout
Version 4.0	18May2020	The following changes have been made: • Removed: o use of Google drive; replaced with UNC OneDrive • Typographical, formatting, and grammatical errors corrected throughout
Version 5.0	09Jul2020	Replacing UNC OneDrive with Google Drive due to technical issues.
Version 6.0	15Dec2020	The following changes have been made: • Updated order of study outcomes • Typographical, formatting, and grammatical errors corrected throughout
Version 7.0	16Nov2021	Updated study outcomes

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1 BACKGROUND AND RATIONALE

Hepatitis C viral (HCV) infection has a tremendous impact on individual and public health. HCV affects over 3 million Americans, leading to 15,000 deaths per year from liver failure, cirrhosis, and liver cancer.[48] Up to 20% of patients will develop cirrhosis[49,50] and 10-20% will develop decompensated cirrhosis or cancer. Though typically associated with the liver, HCV is a multi-faceted systemic disease also affecting multiple organs and systems[51] and associated with many extrahepatic disorders (EHDs) including musculoskeletal, endocrine, neuropsychiatric, and cardiac disorders.[13,52] Our PROP UP data suggest that HCV patients have an average of 4 comorbidities (range: 0-15), the most prevalent being musculoskeletal pain and high blood pressure (50%), psychiatric (44%), sleep disturbance (31%), and diabetes (20%).[53] Patients report clinical distress from somatic and neuropsychiatric symptoms with fatigue, depression, sleep issues and chronic pain most common.[16-20,54] Not surprisingly, HRQOL is impaired.[21,22] While HCV may lead to chronic systemic inflammation with neuropsychiatric and somatic sequalae,[13,54,55] other factors also contribute to poor health including social determinants of poor health.[27] Unhealthy lifestyle habits also perpetuate chronic illness[56-58] and confer greater risk for liver disease, metabolic syndrome, and death.[28,59] Even in patients cured of HCV, many remain symptomatic and at risk for cirrhosis or liver cancer if healthier lifestyles not adopted.[24] The economic burden of HCV is >$10 billion annually when accounting for costs of liver disease, EHDs, low HRQOL and loss of work productivity.[60]

People who have been infected with HCV may benefit from comprehensive multi-modal interventions to improve important patient outcomes. Comprehensive multi-modal psychosocial interventions that provide stress management, coping skills, and lifestyle modification for the HCV population are nonexistent. Despite chronic health risks, multi-morbidities, life stress and unhealthy behaviors, all of which amplify illness, virtually no psychosocial interventions have been developed for the HCV population. However, evidence-based psychosocial interventions have improved diverse health outcomes in people with other chronic illnesses (e.g., cancers, diabetes, chronic fatigue, pain, HIV). Group-based psychosocial interventions that emphasize cognitive behavioral (CB) stress management (SM) coping skills improve psychological and physical health outcomes[30,31,35-37,61] and are associated with change in multiple stress-related immunological indices (e.g., CD4 viral count, cortisol patterns, proinflammatory cytokines).[31-34] Improvements in immune functioning often correlate with symptom reduction.[62-65] In one of the only psychoneuroimmunological studies conducted in HCV, associations were found between patients' depression, anxiety, fatigue, and pain levels and high levels of inflammatory proteins, accounting for up to 40% of the variance in symptoms.[14]

Extrapolating from this strong empirical base built in other chronic diseases, liver disease researchers need to determine if psychosocial interventions confer similar benefits to liver patients. Given the prevalence of HCV and the number of patients who remain symptomatic or may progress to advanced liver disease, comprehensive, holistic liver care should integrate health promotion interventions into current practice, over and above a myopic focus on just viral eradication and medical management of cirrhosis. The ideal intervention would include stress management, coping skills, and health behavior modifications, which, in turn, may improve symptoms, [66] HRQOL, and disease markers.[29,67,68] Within this secondary prevention model, modifying psychological and physiological stress and lifestyle behaviors in symptomatic or at-risk liver patients, may yield substantial health benefits. As such, we sought to tailor evidence-based psychosocial interventions to the needs of HCV patients to improve physical and psychological health outcomes.

Multiple patient barriers exist to attending *in-person* interventions. Patient-level barriers to accessing traditional face-to-face healthcare services are enormous and include travel, geographical, financial, transportation, and illness barriers.[69] This dilemma is particularly salient in rural areas where healthcare access is poor.[39,70] During pilot-testing of the *in-person* group-based Cognitive Behavioral Coping Skills (CBCS-HCV) intervention developed for patients infected with chronic HCV, patients who declined participation cited travel distance and transportation barriers.[6,38] No patients declined due to lack of interest. Many commented that the intervention seemed valuable, but that *in-person* sessions were impractical. Other psychosocial interventions for patients with HCV that require *in-person* sessions have also suffered from low recruitment,[71,72] convincing us that alternative modes of delivery

must be explored to increase access to treatment, especially in rural states like North Carolina (85 out of 100 counties are designated rural).

Delivering interventions via videoconferencing (VC) technology is a cutting-edge alternative to *in-person* delivery. Healthcare delivery is moving rapidly in the direction of utilizing innovative technologies to overcome myriad inefficiencies costs, and barriers that currently stymy the US healthcare system.[39-42] **"**Telehealth" is a burgeoning sector of healthcare delivery in the US. VC technology has numerous potential advantages for delivering interventions directly from providers to patients situated in their own homes.[73] Geographical, financial, and unreliable transportation barriers are eliminated. Patients who are too ill to travel can participate.[74] Reducing patient barriers may lead to higher rates of study enrollment and attendance. Recruitment for *in- person* interventions is often lower than 40%[71], while recruitment for phone- or web-based interventions can range from 57-94%.[7,75-77] Higher attendance may increase intervention "dose," which in turn, may increase clinical effectiveness.[75,78] Patient satisfaction with VC has been shown to be very high and often is preferred over *in-person sessions* due to overcoming many obstacles.[5,75,78,79] Importantly, skill-based psychosocial treatments are commonly delivered in a group format, and can be highly economical and efficient for providers and healthcare systems. Delivering psychosocial skill-based interventions in group formats also capitalize on positive therapeutic processes such as group cohesion, peer support, bonding and social persuasion.[80] In order to retain cost-efficiency and beneficial processes of group-based therapy, an ideal telehealth version of the CBCS-HCV would be delivered via VC technology to a group of HCV patients, *participating from the comfort of their own home.* While many telehealth modalities are being investigated, most are 1:1 provider-to-patient; very few have investigated delivering a group-based intervention to multi-end-user patients in their own separate homes. [2-5]

Since the CBCS-HCV is a skill-based intervention and group format is often the standard of care for these types of interventions, multi-user VC delivery may be a cutting edge and efficient system to deliver holistic interventions to patients who might not otherwise have access to services due to illness or transportation barriers. Pilot testing the CBCS group-based intervention via a state-of-the-art VC multipoint platform is a highly innovative and a logical extension of our previous work. Delivering the CBCS-HCV via VC may decrease patient barriers, increase access to care, and be clinically effective. However, the feasibility, technical issues, patient satisfaction, and preliminary outcomes require pilot-testing to determine if a larger efficacy trial is warranted.

We propose to conduct a pilot feasibility study of a small randomized controlled trial (RCT) to evaluate the CBCS delivered via videoconferencing (herein referred to as "VC-CBCS**"**) compared to patients in standard of care (SC) with a representative sample of 32 symptomatic HCV patients, to address the following specific aims:

2 STUDY AIMS

Aim 1: Evaluate the feasibility of conducting a RCT of the VC-CBCS, quantified as the proportion of patients (a) approached vs. consented vs. enrolled/randomized vs. retained, and (b) who complete data collection;

Aim 2: Evaluate the feasibility of intervention delivery via VC, quantified as (a) the proportion of sessions attended by participants and (b) frequency and nature of technical, logistical, or participant problems;

Aim 3: Evaluate patient acceptability and satisfaction;

Aim 4: Explore changes in patient outcomes, mediators and intervention targets, as well as temporal associations and strength of associations among variables in a preliminary conceptual model, to inform a future efficacy trial.

3 STUDY DESIGN

3.1 Study Design

This pilot feasibility study was designed as a preparatory two-arm small randomized controlled trial (RCT) with a total enrollment of 32 participants assigned by randomization to VC-CBCS (n=24) or SC (n=8) to address the specific aim.

3.2 Study Participants

Participants (n=32) will be a representative sample of adult patients, age 21 or older, who have or had a diagnosis of chronic HCV

3.3. Inclusion/Exclusion Criteria

3.3.1. Inclusion

- Age 21 and older;
- Medically cleared by hepatology;
- Patients who are currently or were previously diagnosed with chronic HCV;
- Evidence of ongoing symptoms, stress, or unhealthy lifestyle habits, defined as a score of greater than or equal to 4 on a scale 0(none) - 10 (severe) on two or more numeric rating scale questions (see Screening Form 1);
- Able to read and speak English.

3.3.2. Exclusion

- Decompensated liver disease (Childs Pugh C) judged by hepatologist or recorded in patient medical record;
- Life expectancy of <12 months estimated by hepatologist;
- Has had a liver transplant or is on the waitlist for a transplant;
- Severe alcohol or substance use disorder, psychiatric disorder or cognitive impairment that is likely to interfere with the ability to participate in telehealth groups and follow guidelines about group participation as judged by the Hepatology provider or research staff using a two-tiered research screening process (See Section 6);
- Lack of private, quiet space in home in which to participate in VC-CBCS sessions; and
- Unwilling to have group sessions audio-recorded.

4 RECRUITMENT

A two-pronged recruitment strategy will be utilized (primary: in person in liver clinic; secondary: over the phone). Patients will be recruited from the outpatient liver clinics or by phone if referred by a hepatology provider.

For every patient approached for recruitment, a minimal amount of data will be stored in a REDCap Screening Database, separate from the REDCap Research Database. The Screening Log will include: name, MRN, phone number, race, sex, age, and reason for exclusion or not proceeding forward with consent process. Name, MRN and phone number will be deleted after recruitment ends. De-identified race, sex, and age are retained to satisfy CONSORT guidelines for future publications.

Patients will be recruited in 4 waves. Although we seek to enroll/randomize a total of 32 patients with 24 randomized to VC-CBCS and 8 randomized to SC, we will over-consent to accommodate for patients who are deemed ineligible during the screening process or who withdraw consent prior to enrollment. The overall 3:1 randomization scheme allows us to examine feasibility of randomization while allowing us to intensively examine the VC-CBCS group.

5 INFORMED CONSENT PROCESS

The informed consent process will take place in person in the GI liver clinic or over the phone.

1. **In-Person Consent**: Interested patients will be introduced to study staff and taken to another private room to engage in the informed consent process and screening assessment. Interested and eligible patients will sign and date/time the consent forms, staff signs/dates and the patient will be provided a copy. The informed consent process will be documented for each consented patient. After written consent is obtained, staff can begin to screen and collect data from the patient.
2. **Over-the-Phone Consent**: When a prospective patient is referred by a hepatology provider to the study team, the staff will pre-screen the patient using a limited waiver of HIPAA approved by the UNC IRB. Study staff will access patient medical records for contact information and conduct a brief eligibility assessment (e.g., HCV diagnosis, > age 21, English speaker). Staff will contact patients via phone to discuss the study and consent documents. Interested patients will be consented with a verbal telephone consent and then be emailed or mailed a HIPAA authorization with a pre-paid envelope for return. The study team will then review the HIPAA authorization with the participant and instruct the participant to sign and date and return to study in provided envelope. Participants will be considered consented if and when they agree to the telephone verbal consent, but their medical records will not be accessed until signed HIPAA authorization is received by the study team.

Whether consented in-person or over the phone, all components of the informed consent process will be reviewed and documented per federal (https://www.hhs.gov/ohrp/regulations-and-policy/regulations/finalized-revisions-common-rule/index.html) and institutional guidelines (https://www.hhs.gov/ohrp/regulations-and-policy/regulations/finalized-revisions-common-rule/index.html) and relevant Good Clinical Practice Guidelines from the International Conference on Harmonisation. Issues of privacy, confidentiality, and time commitment will be discussed. Patients will verbalize understanding that research participation in voluntary and they can choose to stop or decline at any time without penalty. They can refuse to participate, and this decision will not affect their medical care at UNC. They can refuse to answer any study or interview question. The study staff obtaining consent will allow ample time for patients to ask questions and express full understanding of the study.

A checklist of the informed consent process will be retained for all consented patients. All signed consent forms will be uploaded to the REDCap database and hard copies retained in a secure location. Data collection, enrollment, randomization will not commence until all necessary consents have been obtained.

Patients will consent to participate in the following:
1) review of electronic medical records for clinical data;
2) undergo screening process and collection of screening data;
3) participation in a 14-week VC-CBCS group intervention delivered via home technology or study-loaned tablets that patients may return at the end of the study;
4) participation in a group exit interview following participation in the intervention;
5) completion of self-report surveys throughout the study;
6) collection of saliva samples at pre- and post-intervention; and
7) REDCap storage of email address, mailing address, phone numbers for self and a loved one in case of lost to follow-up. This information is required for REDCap data collection of surveys, reimbursement to patients and communication throughout the study.

6 SCREENING FOR VC-CBCS ELIGIBILITY

To enhance intervention fidelity, group cohesion/dynamics, and adherence to the protocol, a two-tiered screening process will be conducted to enroll eligible patients. Patients will be consented prior to engaging in the screening assessment. Phase I of screening will occur with study staff in-person in the liver clinic or over the phone. Phase II is conducted by the study PI.

6.1 Phase I Screen: Staff will conduct the initial screening for I/E criteria using three Screening Forms located in a separate REDCap database for screening data only. The patient must meet all inclusion criteria including "evidence of ongoing symptoms, stress, or unhealthy lifestyle habits as defined by a score of ≥ 4 on a rating scale from 0 – 10, for ≥ 2 symptoms, perceived stress, or lifestyle habits" and must not meet exclusion criteria, including severe current alcohol, substance use or psychiatric disorder likely to interfere with group dynamics or adherence to study protocol. The Screening Forms will include items to determine inclusion/exclusion criteria, including assessment of physical and mental symptoms, stress level, and lifestyle habits. Alcohol, substance use, and psychopathology will be assessed using questions from validated instruments, including the Alcohol Use Disorders Identification Test (AUDIT), the Substance Abuse and Mental Illness Brief Symptom Screener (SAMISS) and additional screening items developed by the PI. Screening will take place in-person in private exam room in clinic, or over the phone.

6.2 Phase II Screen: The second phase of the two-tiered screening process will be conducted by the PI (a licensed clinical psychologist at UNC Healthcare) who will review the Phase I screening forms and discuss the prospective participant with the screening coordinator who conducted the consent and screen. If the patient meets I/E criteria and screens negative for severe current alcohol, substance use or psychiatric disorders, the patient will be approved for enrollment into the study based on Phase I screening data. When ambiguity or uncertainty arises regarding the patient's eligibility related to current alcohol, substance use or psychiatric disorders, the PI will conduct a brief clinical interview with a prospective participant over the phone. Based on the two-tiered screening process, the PI will adjudicate final decisions regarding study eligibility.

The goal of the two-tiered screening process is to ensure that patients (1) are appropriate for a group therapeutic setting; (2) are at low risk for verbal behaviors that will interfere with or sabotage group cohesiveness/support which is critical to the success of psychosocial interventions; (3) are able to adhere to the study protocol and rules of engagement; and (4) with active and severe psychiatric or substance use disorders are referred for more appropriate individual treatment in their local community.

Patients judged to have untreated or more severe psychopathology will receive a referral from the PI to more appropriate mental health/addiction services in their local community.

6.3 Screening Data: Data from the three Phase I Screening Forms will be stored in a REDCap screening database separate from the Research Data. For patients who are ineligible or decline to participate, their name, MRN, age, sex, race, and reason for ineligibility/refusal will be retained in the screening REDCap database. All other screening data will be deleted at the end of the study. Name and MRN are retained during the study for staff to identify previously recruited but ineligible patients. Name and MRN of non-enrolled patients will be deleted from the screening database after recruitment ends. The hard copy Phase II Brief Clinical Interview forms will be shredded after recruitment ends. Once the screening data are deleted or de-identified, only sex, race, age, and reason for non-enrollment patients will be retained until all data are published, to satisfy CONSORT guidelines. Once final data are published, the REDCap Screening database will be deleted. For patients who are eligible and enrolled, data from the three Screening Forms will be exported into the Research REDCap database to describe characteristics of the cohorts.

7 REIMBURSEMENT

Participants in both conditions will be reimbursed $25 for four patient-reported outcomes (PROs) assessments and two days of salivary sample collection. Completion of PROs during each assessment period will take 20-30 minutes. Patients randomized to VC-CBCS will be reimbursed $25 to participate in an exit focus group. For reimbursement of VC-CBCS sessions, participants will be reimbursed for cellular and wi-fi data plans, if needed for iPad use, and will be given two options: (1) retain the iPad (worth $300) after the study ends; (2) receive a rechargeable Visa gift card at the beginning of the study that will be recharged with $300 after the intervention ends and iPad is returned. Participants will check their preference for one of these two options on the consent form. Participant preferences will be tracked in a Reimbursement Log to inform reimbursement options for a future RCT.

8 RANDOMIZATION

Four groups of patients will be randomized and will consist of 7-9 patients each. The groups are as follows:

- Group 1 - 7 patients with 5 randomized to VC-CBCS and 2 to SC;
- Group 2 - 9 patients with 7 randomized to VC-CBCS and 2 to SC;
- Groups 3 and 4 - 8 patients each with 6 randomized to VC-CBCS and 2 to SC each group.

Once each group meets their respective necessary number of patients, they will be randomized. We will use these randomization procedures for a total of 24 participants randomized to VC-CBCS and 8 randomized to SC and overall 3:1 ratio. A computer-based procedure for permuted-block randomization and concealment will be implemented by non-study staff. No study personnel will have access to the randomization schedule. The computer-generalized randomization scheme will automatically randomize patients who are enrolled to one of the two group assignments after each wave is enrolled. Participants will be subsequently called and informed of group assignment.

9 STANDARD CARE

Patients randomized to the SC condition will be managed per standard HCV and liver disease management guidelines by the UNC hepatologists. Clinic appointments, lab tests and procedures will be conducted at the provider's discretion. Depending on severity of liver disease, patients are typically followed every 6-12 months by Hepatology. Research staff will have minimal contact with SC participants except during PRO assessment windows and two saliva sample collections. Study staff will extract clinical data from electronic medical records up to 6 months post-intervention.

10 VC-CBCS GROUP INTERVENTION

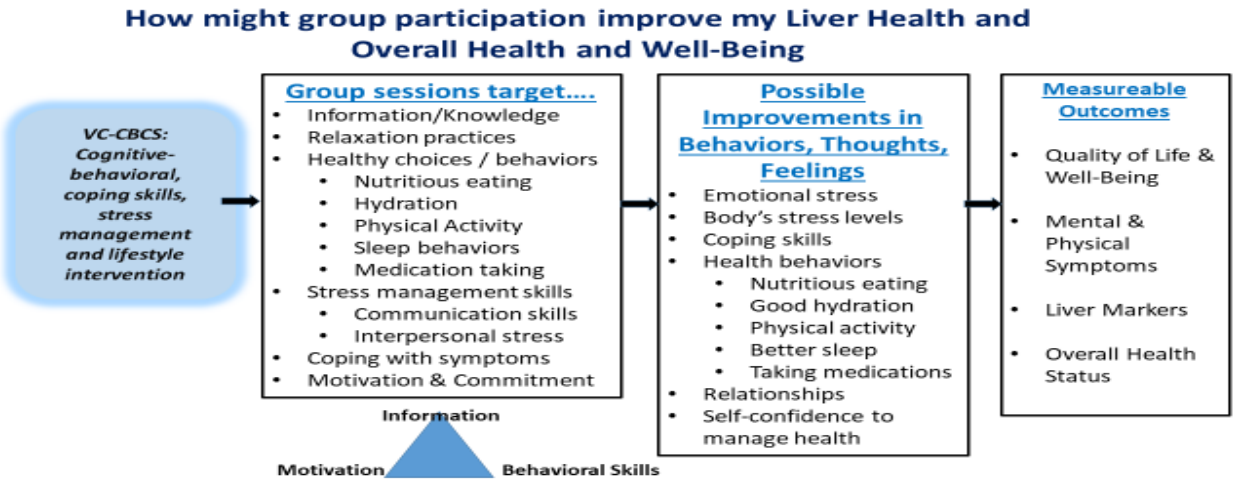
The CBCS is based on Cognitive Behavioral Theory (CBT) and the Informational-Motivation-Behavioral skills (IMB) theoretical framework.[83,97,101] The intervention modules will be delivered over 14 sessions, each with a duration of 90 to 120 minutes to allow for the practice of a newly introduced skill. Each session will incorporate comprehensive information on evidence-based skills for health behavior change and stress management. The modules will also incorporate CBT skills and educational materials developed by federal agencies.[102-104] Sessions will include background information and rationale, recommended behavioral skills and will utilize strategies such as peer discussion and support, goal-setting and motivational enhancement techniques to increase commitment and motivation for positive lifestyle changes.

10.1 Tentative Conceptual Model of the VC-CBCS

As a pilot feasibility study, we are not *testing* the intervention model depicted in **Figure 1** below. We are mapping out a hypothetical model to gather preparatory information to inform a subsequent efficacy trial: The model helps to identify survey items that need to be developed or used to measure intervention targets and mediators. Pilot-testing will help determine the optimal frequency of data collection of targets and mediators while balancing patient burden. Pilot-testing will help with exploration of preliminary associations (aim #4) among variables to understand their temporal relationships and strength of associations. **Figure 1** describes how each intervention session will attempt to target information-motivation-behavioral skills (CBT, stress management, health behaviors). Didactic information is provided to build 'buy-in'. Behavioral skills are taught and practiced during session and as homework. Sessions wrap up with round robin discussion of patients' SMART goals for the week and why a patient is motivated to work on this goal (fosters personal and social motivational enhancement, commitment, social persuasion, and healthy norms). Intervention targets may improve both psychological and physiological stress, healthy behaviors, and medication adherence, which may operate as mediators/mechanisms of change, but may also serve as intermediate outcomes in and of themselves. These mediators or intermediate outcomes may in turn, improve health outcomes, including overall health status and symptoms. It is plausible that behavioral changes and stress reduction may improve clinical disease outcomes. In this pilot study, we will attempt to collect aspartate aminotransferase (AST) and alanine aminotransferase (ALT) from patients electronic health records (EHRs) to determine the feasibility of collecting standard clinical data from the EHRs, and if

feasible, explore potential pre-post change in these two markers of liver inflammation. We will also extract additional clinical variables of interest that may be relevant to a future efficacy trial, such as hemoglobin A1C in diabetic patients (~ 20% of sample), body weight (kg) and other laboratory tests. If a future efficacy trial finds the VC-CBCS to have short-term benefits on patient outcomes, it would behoove us to investigate the potential for longer-term benefits on subjective health, liver disease, and other comorbid conditions, as has been shown in other medical populations.[106-109]

Figure 1: Conceptual Model of VC-CBCS Intervention



10.2 Conducting the VC-CBCS Group Intervention

Sessions will be delivered using the UNC School of Medicine's University-approved, HIPAA-compliant WebEx® videoconferencing system. WebEx® is an application that is widely used for web and videoconferencing meetings and includes multi-point audio and video communication, screen sharing, video and audio recording, and telephone bridging. The research team will work closely with the UNC School of Medicine Information Technology Security Team on all aspects of delivering the VC-CBCS including patient instructions, iPad set up, and remote data cleaning. Each group member will join the virtual group from their home using their choice of home audio-visual technology or study-provided iPads to simultaneously observe and interact with the group facilitator and other group members ("Brady Bunch" style).

All modules follow the same three-part organization (**Table 1**):
(1) Introduction and practice of new relaxation skill
(2) Review of previous weeks' information, skill, and SMART goals
(3) Information, acquisition, and practice of new skills. Didactic information is followed by practicing skills to aid in cognitive behavior change. Motivational enhancement strategies are used to increase personal and social motivation.[97,101] SMART goals are used to promote achievement of weekly goals that are specific, measurable, action-oriented, realistic, and time-based.

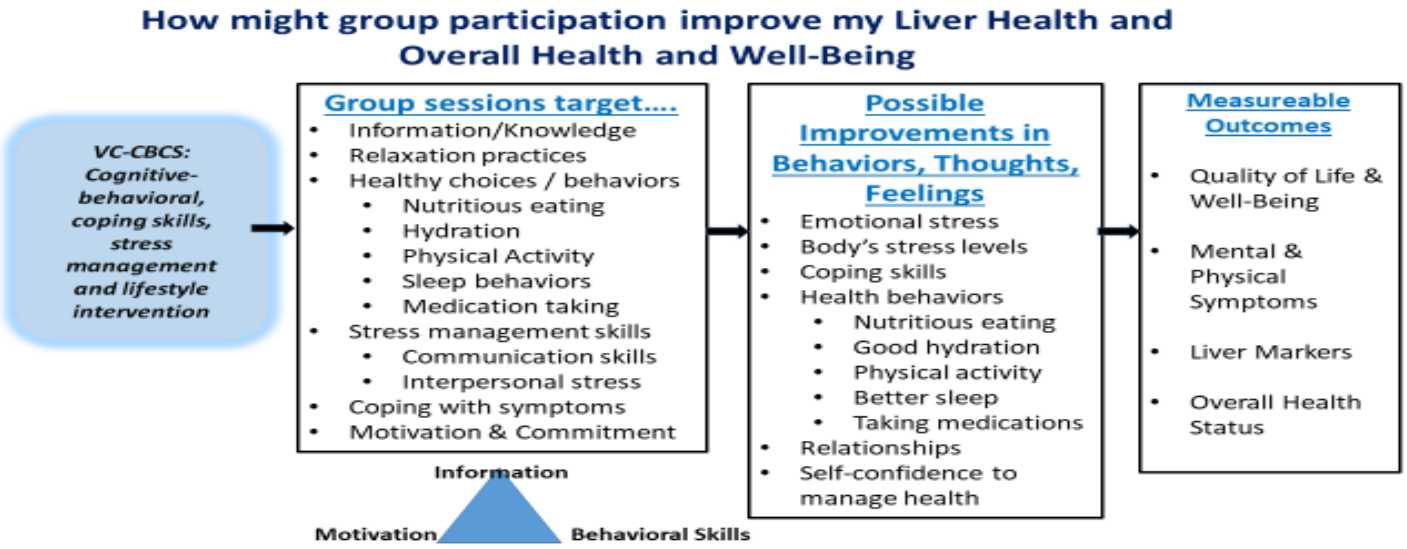
VC-CBCS sessions will be led by a Masters-level therapist with experience in facilitating groups, protocol-based and evidence-based treatments, and adept at motivational enhancement strategies.

VC-CBCS patient materials will be stored on iPads and uploaded to a secure Google Drive shared drive containing no identifying information. Materials include the Patient Workbooks, relaxation audio-recordings, technical instructions, and link to unique REDCap application system. Hard copy *Patient Workbook*s will also be mailed to each participant prior to the first session for use during sessions.

Table 1: Content and structure of 14 VC-CBCS group modules

Mod	Part 1: Relaxation Training	Part 2: Review and Application of Previous Skills	Part 3: Training in New Topic and Skills
1	Progress. Muscle Relax. (PMR-6)	Introductions, Group Expectations; Confidentiality	Overview of Liver Functions, Liver Conditions, and Targets of the VC-CBCS Intervention
2	Diaphragmatic Breathing & PMR-4	Overview of Liver Functions, Liver Conditions, and Targets of the VC-CBCS Intervention	Love Your Liver: Healthy Nutrition and Hydration
3	Diaphragmatic Breathing & Mindfulness	Love Your Liver: Healthy Nutrition and Hydration	Physical Activity for the Liver
4	PMR-4 & Healing Wellness Imagery	Physical Activity for the Liver	Sleep Hygiene & Managing Sleep Problems
5	Diaphragmatic Breathing & Light Imagery	Sleep Hygiene & Managing Sleep Problems	Taking medications as prescribed & Maintaining Healthy Lifestyle
6	Deep Breathing & Immune Guided Imagery	Taking medications as prescribed & Maintaining Healthy Lifestyle	Stress Awareness & Appraisal
7	Diaphragmatic Breathing & Autogenic Training	Stress Awareness & Appraisal	Automatic Thoughts & Cognitive Distortions
8	PMR-4 & Self-Forgiveness Affirmation Script	Automatic Thoughts & Cognitive Distortions	Cognitive Restructuring
9	Counting Breaths & Passive PMR	Cognitive Restructuring	Coping with Stress & Symptoms
10	4-7-8 Breath & Mindful Movement	Coping with Stress & Symptoms	Cognitive-Behavioral Skills for Depression - Behavioral Activation & Pleasurable Events
11	Short Body Scan	Cognitive-Behavioral Skills for Depression – Behavioral Activation & Pleasurable Events	Activity-Rest Cycles
12	Mini Practices & Self-Acceptance Affirmation Script	Activity-Rest Cycles	Anger Prevention & Management
13	Mindfulness Meditation & Deep Breathing	Anger Prevention & Management	Assertive Communication; Interpersonal Effectiveness
14	Group Choice	Assertive Communication; Interpersonal Effectiveness	Maintenance of Positive Lifestyle Changes & SMART Goals; Group Program Review

Figure 2: How does the VC-CBCS help to improve Liver Health and Wellness?



10.3 Technology Training and iPads and Review of Rules of Group Engagement and Privacy

If patients do not have appropriate audio-visual technology on home computers/laptops, they will be provided a study iPad and funding for cellular or internet data plans during the duration of the study. The UNC School of Medicine Information Technology Services (ITS; https://its.unc.edu/) staff and the national broadband map (https://www.broadbandmap.gov/) will be used to determine best data plans for each participant. The iPads will be set-up and secured by SOM ITS. Participants will receive iPad, internet, and REDCap data collection training from the research staff with ITS support prior to the initial session. A conference line will be available if VC disconnection occurs. All technical issues will be tracked as part of reporting feasibility outcomes. Our consultants will share best practices for delivering tele-mental health.[45,105] An SOM ITS expert will be available during each cohort launch to troubleshoot. Although patients will be provided iPad and data plans, WebEx® is available for Android and iOS smart phones. A few patients may be allowed to participate via smartphone to examine patient satisfaction and outcomes using smartphones, which could be more scalable in future projects. They can complete their post-session surveys at the conclusion of each session or at their convenience during the assessment window (7 days).

During the WebEx® training with study staff, privacy and confidentiality issues related to engagement in home-based virtual groups with other participants will be thoroughly discussed. A copy of group rules will be reviewed. Participants will need to provide verbal assurance that they will respect the group privacy rules.

10.4 Iterative changes to VC-CBCS intervention

Based on patient feedback and lessons learned, the research team will modify aspects of the VC-CBCS in-between the four waves. Changes may be made based on feasibility data, patient satisfaction ratings, and impromptu feedback, feedback from exit focus groups and overall experiences and lessons learned. Consideration for making *substantial* changes during the trial would occur if major issues were identified that seriously jeopardize recruitment, attendance, retention, or data collection efforts. Otherwise, we will carefully track issues during each wave, making minor changes to improve performance, and solicit feedback about issues during exit focus groups. If recruitment, attendance, and retention are not hugely jeopardized, the team may wait to make substantive changes until after all the feasibility, patient acceptability, and exit focus group data are analyzed.

11 DATA COLLECTION ASSSEMENT SCHEDULE

The data collection assessment schedule is shown in Table 2.

11.1 PRO Assessments

In both conditions, PRO survey data will be collected directly from patients during the following assessment periods:

T1: Pre-intervention (time period: Within 30 days prior to start of 1st intervention session);
T2: After the 5th intervention session (time period: Within 21 days after the 5th session);
T3: After the 10th intervention session (Time period: Within 21 days after the 10th session); and
T4: At post-intervention after the 14th session (Time period: within 14 days after the 14th session).

11.2 Salivary Cortisol

Saliva samples will be collected from participants in both conditions pre-intervention and post-intervention as described below. Pre-intervention time period is within 7 days prior to 1st intervention session. Post-intervention time period is within 7 days after final 14th intervention session.

11.3 VC-CBCS Process Assessments

In participants assigned to the VC-CBCS condition, they will submit self-report data directly into REDCap after each of the 14 intervention sessions to collect process data. Data collected will include Patient Satisfaction/Acceptability Ratings; S-M-A-R-T (specific, measurable, action-oriented, realistic, and time-based) goals; Ratings of Importance, Motivation and Self-Confidence related to each SMART goal.

Table 2: Data Collection Schedule

Table 2	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1. Study Feasibility															
# approached to consented	X														
# consented to eligible	X														
# eligible to enrolled/randomized	X														
# enrolled/randomized to retained	X														X
Randomization	X														
Session Attendance		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Data Collection	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Technology/Logistical Problems	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
2. Patient Satisfaction															
Patient Acceptability		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Reasons for drop out		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Group Dynamic Survey						X									X
Exit Focus Groups															X
3. Protocol Fidelity															
Facilitator Adherence		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Facilitator Competence		X	X	X	X	X	X	X	X	X	X	X	X	X	X
4. Patient Features															
NINR sociodemographic data	X														
Screening information	X														X
Clinical / lab data	X														X
5. Intervention Targets	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
6a. Intermediate Outcomes/Mediators	X					X					X				X
6b. Salivary Cortisol	X														X
7a. PROs	X					X					X				X
7b. Liver enzymes / clinical data	X														X

12 MEASURES TO EVALUATE FOUR SPECIFIC AIMS

12.1 Study and Intervention Feasibility (Aims #1, #2)

To address specific aims #1 and #2, several feasibility measures will be collected from all participants. To evaluate the feasibility of conducting a larger RCT of the VC-CBCS, we will collect data on the proportion of patients who are approached/contacted by study staff ($N^{approached}$) vs. consented ($N^{consented}$) vs. randomized/enrolled ($N^{R/E}$) vs. retained ($N^{retained}$). Feasibility of data collection, EHR extraction of clinical data, and frequency and patterns of missing data on various outcomes will be evaluated (i.e., PROs, process/intermediate outcomes, salivary samples, clinical/disease outcomes). To evaluate the feasibility of delivering the intervention via video technology, we will collect feasibility data on the proportion of sessions attended by VC-CBCS participants, have patients complete a telehealth satisfaction survey, and track the frequency and nature of technical, logistical, and participant problems.

12.2 Patient Satisfaction (Aim #3)

To address specific aim #3, several measures of patient satisfaction will be collected. VC-CBCS patients will complete a Patient Acceptability/Satisfaction survey after each of the 14 sessions.[6] They will complete a survey on satisfaction with therapist and group dynamics midway through and at end of the intervention.[6,99,110,111] Reasons for drop out and attrition will be evaluated in both conditions. Exit group interviews will be conducted with each VC-CBCS cohort after the intervention ends and will be audio-recorded. The audio recording will be stored on a secure network server housed by UNC. The qualitative data will be analyzed to understand likes/dislikes, pros/cons, and solicit feedback on optimizing the intervention (e.g., number and duration of sessions, modules, relaxation skills, structure, group format, data collection). For the Patient Acceptability/Satisfaction Survey, items are scored on a scale from 1= not at all to 5=extremely. Data across all patients and all sessions will be averaged into a Total Patient Satisfaction

score that could range from 1 to 5 with higher scores indicating greater satisfaction. *One secondary outcome is the overall Patient Acceptability/Satisfaction survey mean score from all patients over all 14 sessions.*

12.3 Patient-Reported Outcome Measures (Aim #4)

To address specific aim #4, several PRO measures will be collected to evaluate primary, secondary and exploratory outcomes to examine the temporal associations and strength of associations among variables in the preliminary conceptual described in Figure 1. PROs will be collected from all participants at four PRO time points (T1-T4). Collection of PRO data serves several preparatory functions for the efficacy trial including making final selection of PROs, contributing to sample size calculations, and exploring preliminary relationships with other variables in the causal pathway.

13 PRIMARY FEASIBILITY OUTCOME MEASURES

13.1 Percentage of Patients Consented Versus Approached
13.2 Percentage of Participants Consented Versus Randomized
13.3 Percentage of Standard of Care Condition Participants Retained vs Enrolled
13.4 Percentage of VC-CBCS Intervention Condition Participants Retained vs Enrolled
13.5 Percentage of Surveys Completed by Participants Who Completed the Study

14 PRIMARY PATIENT-REPORTED OUTCOME MEASURES

Several of the NIH Patient-Reported Outcomes Measurement System (PROMIS®) short forms will be used to measure primary outcomes such as health status, mental health symptoms, and physical health symptoms. We have found the PROMIS® surveys to have good psychometrics in HCV patients.[124] *The primary patient-reported outcomes will be the mean T-scores at T1 (Baseline) and T4 (end of intervention):*

14.1 PROMIS Global Health Status Mental Health Mean T-Score
14.2 PROMIS Global Health Status Physical Health Mean T-Score
14.3 PROMIS Depression Mean T-score
14.4 PROMIS Anger Mean T-score
14.5 PROMIS Anxiety Mean T-score
14.6 PROMIS Fatigue Mean T-score
14.7 PROMIS Sleep Disturbance Mean T-score
14.8 PROMIS Pain Interference Mean T-score

15 SECONDARY PATIENT-REPORTED OUTCOME MEASURES

15.1 The Perceived Stress Scale Mean Score (PSS) measures perceived stress in all participants at four PRO time points (T1-T4) and covers 30 days prior to assessment.[115] The PSS is a widely used survey to measure stress perception. The scale includes 10 items, rated using a 5-point scale, from 0 (never) to 4 (very often) where patients report the frequency of stress symptoms in the past month. Higher PSS scores reflect higher subjective stress.

15.2 Sleep Behaviors

15.2.1 Pittsburgh Sleep Quality Index (PSQI) measures sleep behaviors and issues.[117] All participants complete this measure at PRO time points T1 and T4 that covers 30 days prior to assessment. "During the past month, how would you rate your sleep quality overall?" The response set ranges from a minimum of 0 (Very Good) to a maximum of 3 (Very Bad). Higher mean scores indicate worse sleep quality.

15.2.2 Pittsburgh Sleep Quality Index (PSQI) Sleep Efficiency Composite Mean Score. Items 1, 3 and 4 from the Pittsburgh Sleep Quality Index (PSQI) were used to create a Sleep Efficiency composite score. All participants completed this measure at T1 and T4 that covered 30 days prior to assessment. The sleep efficiency score = (# hours slept/# hours in bed) X 100% .The sleep efficiency composite

score ranged from: 0 = >85% efficiency,1 = 75-84% efficiency, 2= 65-74% efficiency, and 3= <65%. Lower scores indicate better sleep efficiency.

15.2.3 Healthy Sleep Behaviors Mean Score. One item "In the last month, how often did you engage in healthy sleep behaviors before bedtime?" evaluated healthy sleep behaviors. All participants completed this measure at T1 and T4. The response set ranged from 0 (not at all) to 4 (almost every night). Higher scores indicated better sleep behaviors.

15.3 Medication Adherence Visual Analog Scales evaluate medication adherence for up to five daily medications for multiple comorbidities in the past 7 days in participants who were prescribed medications at baseline. Participants report the average adherence over the course of 7 days for each medication on a scale from 0% to 100% adherence for each medication.

15.4 Coping Skills Confidence Mean Score: Items from the Measure of Current Status (MOCS)-Part A will measure patient confidence in performing multiple skills including stress awareness, relaxation, assertiveness, and coping skills.[114] The Measure of Current Status (MOCS)-Part A will measure patient confidence in performing multiple skills including stress awareness, relaxation, assertiveness, and coping skills. The scale contains 13 items rated on a scale from 0 = I cannot do this at all to 4 = I can do this extremely well. A Total Coping Skills score is created by taking the average of the 13 items where the Total Coping Skill score can range from 0 to 4.

15.5. Alcohol and Drug Use: Items from the Substance Abuse and Mental Illness Symptoms Screener (SAMISS) Survey evaluate self-reported alcohol use (3 items), non-prescription street drug use(1 item), and prescription drug misuse (1 item) in all participants. Individual scores could range from 0 to 4, with higher reported mean scores indicating higher consumption.

15.6 Behavioral Risk Factor Surveillance System (BRFSS)[116] items measure health behaviors such as exercise; fruit, vegetable, added sugar and sweet beverage consumption; meals prepared at home in all participants at T1 (baseline) and T4 (Week 14) and will cover 30 days prior to assessment. BRFSS items were used to measure the following secondary outcomes:

15.6.1 Percentage of Participants Who Improved Fruit Consumption by One or More Categories
15.6.2 Percentage of Participants Who Improved Vegetable Consumption by One or More Categories
15.6.3 Percentage of Participants Who Complete Moderate Activity for at Least 10 Minutes at a Time
15.6.4 Mean Number of Minutes of Moderate Activity Per Week
15.6.5 Percentage of Participants Who Complete Vigorous Activity for at Least 10 Minutes at a Time
15.6.6 Mean Number of Minutes of Vigorous Activity Per Week
15.6.7 Mean Time Spent Sitting on the Weekdays
15.6.8 Mean Time Spent Sitting on the Weekends
15.6.9 Percentage of Participants Who Reduced Regular Soda Intake by One or More Categories
15.6.10 Percentage of Participants Who Reduced Diet Soda Intake by One or More Categories
15.6.11 Percentage of Participants Who Reduced Meals from Fast Food Restaurants by One or More Categories
15.6.12 Percentage of Participants Who Increased Dinners Prepared at Home by 1 or More Days

15.7 Participant Satisfaction With VC-CBCS Intervention Mean Score: After each VC-CBCS intervention session, participants complete a 14-item acceptability/satisfaction survey about their impressions with the current intervention session. Items are scored on a scale from 1= not at all to 5=extremely useful. Data across all VC-CBCS participants and all intervention sessions are averaged into a Total Patient Satisfaction score that could range from a minimum of 1 to a maximum of 5 with higher scores indicating greater satisfaction.

15.8 Weight Changes. Change in raw weight, percent weight change, and BMI evaluated among those who had pre-intervention BMI > 24.9 (overweight and above) from T1 to T4.

16 SECONDARY CLINICAL OUTCOMES

Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are extracted from all participants electronic health records (EHRs) who had already achieved viral cure at baseline and who were not on HCV treatment at baseline in order to determine feasibility of extracting these data from the medical record

and explore pre and post intervention mean scores in these two markers of liver inflammation. Mean AST and ALT levels are compared in both females and males.

17 EXPLORATORY PATIENT-REPORTED OUTCOME MEASURE

17.1 Satisfaction with Telehealth Session Mean Score. After session 1 and session 14, participants complete a 15-item acceptability/satisfaction survey about their satisfaction with using telehealth sessions. Items are scored on a scale from 1= strongly disagree to 5=strongly agree. The average Total Telehealth Satisfaction score is analyzed from session 1 and session 10, which could range from 1 to 5 with higher scores indicating greater satisfaction.

18 EXPLORATORY STRESS BIOMARKER OUTCOME

Participants in both conditions collect saliva samples at baseline (T1) and post-treatment (T4). Cortisol secretions follow a diurnal pattern, but physiological and psychological stress disrupt normal rhythms, dysregulate the sympathetic nervous system and HPA axis and are associated with poor health. Conversely, stress management skills regulate cortisol patterns.[32,92,118-120] Participants will be given two salivary collection kits to provide salivary samples pre- and post-intervention. Participants will provide salivary samples four times: immediately upon wakening, 30 minutes after awakening, in the late afternoon, and at bedtime. Research staff will contact patients the day prior to collection to remind them of the protocol. Samples will be stored in participants' home refrigerators within 30 minutes of collection and mailed to UNC in pre-paid gel wrap mailers. Samples will be stored at −80°C until assayed. Collection and storage methods have been validated.121 Saliva samples will be stored de-identified using subject ID number only. Mean $\log_{10}$ cortisol as a diurnal function of time of day and summary values such as the area under the curve (AUC), AUC minus ground will be compared from T1 to T4. Lower cortisol levels indicate a lower level of stress**.**

19 INTERVENTION TARGETS

VC-CBCS participants will complete a weekly Post-*Intervention* Form after each of 14 sessions directly into REDCap on their iPad or home technology.

19.1 SMART Goals related to health changes, stress management, and cognitive-behavioral skills. After each new session, each patient will describe at least one new SMART goal related to the session topic such that after session one, they describe one goal…after session 14, they describe 14 goals, one per topic.

19.2 For each SMART goal, patients will rate the *Importance/Relevance* of the particular goal, their *Motivation* to achieve the goal, and their *Self-Efficacy* to achieve the particular goal. The three ratings will be on a Numeric Rating Scale ranging from 0% to 100%.

20 PATIENT SOCIODEMOGRAPHICS

At baseline (T1), all participants will self-report the following NINR data elements: age, sex, race, ethnicity, marital status, income, education level, employment status, caregiver type, household member total count, and health comorbidities.[112-114] History of psychiatric, alcohol and substance use issues will be obtained during the screening process and transferred to the research database for enrolled patients. All data will be cross-validated with data reviewed in patients' EHRs.

21 PROTOCOL FIDELITY

To examine the Group Facilitator's competency and fidelity to the intervention protocol and 14 modules, we will utilized two observer-rating forms to evaluate Facilitator Adherence and Facilitator Competency to manage group dynamics. A research staff member will observe VC-CBCS sessions and complete the observer-rating Facilitator Adherence form, rating the proportion of sections completed on scale of 0-100%. The staff member will also complete the Facilitator Competency observer-rating form, a 14-item Likert

scale (1=not at all; 4=extremely). The Facilitator will not have access to these ratings until completion of each cohort.

22 ELECTRONIC DATA CAPTURE AND SECURE STORAGE

Data will be directly entered and stored in the web-based research electronic data capture system, REDCap (https://projectredcap.org/). The REDCap system is a secure, HIPAA-compliant web-based application to support distributed data collection governed by standard University, School of Medicine, and Federal information security policies and standards. The REDCap application is hosted and monitored on a secure server located within the UNC CTSA-funded NC TraCS Institute's Bioinformatics Core. Access to the REDCap database for this study will be restricted to authorized research team members as needed to perform their job functions. Research staff who access the REDCap system will use a unique user ID provided by the Bioinformatics Core. Research staff will enter EHR data into clinical forms on REDCap. Each time research staff access REDCap, a unique electronic signature (login) is required, and REDCap maintains an audit trail of all activity. Participants will be given the choice of providing PRO data (a) directly into REDCap from a weblink set up on their iPad, (b) from an automated email from the REDCap system that contains a URL link to the survey or (c) through phone-delivered surveys with study staff who enter responses directly into REDCap. Each REDCap link is unique to each subject and each assessment period. Patients will be sent electronic reminders from REDCap to approved email addresses when PRO data entry is needed.

For each consented patient, their consent documents will be uploaded and stored in REDCap. Hard copy consent documents will be stored in a secure location.

While the research data will be stored in REDCap, other study materials (e.g., SAE/AE forms, reimbursements, audio-video recordings) will be securely stored on VPN- and password protected CGIBD secure server in a study folder. The server and study folders are maintained and monitored by UNC SOM ITS. ITS will provide access only to staff working on this project. No study-related documents containing patient PHI or identifiers will reside on desktop or laptop computers.

23 DATA ANALYSIS

23.1 Statistical Analysis Overview

The analysis strategies are designed to inform the feasibility and planning of a subsequent efficacy RCT. No hypothesis tests will be conducted. Statistical estimates will be reported with 95% confidence intervals (CIs) or standard deviations. Collectively, the results of this preparatory study will allow us to formulate reasonable expectations for the subsequent RCT. A publicly available PROMIS® scoring system is available for computing PROMIS T-scores. Statistical computations will be performed in SAS software (SAS Institute, Cary, NC).

23.2 Aim 1: Feasibility of conducting a RCT

Frequencies will be tabulated for the following: patients approached/called, consented, randomized/enrolled, retained, completed surveys, and salivary cortisol samples. We will examine reasons for refusal, causes of dropout, session attendance, causes and patterns of missing data, and technical and logistical difficulties with delivering the intervention via VC. *We anticipate that >50% of approached/called patients will consent; >75% of consented patients will be randomized and enroll; >80% will be retained; and >90% of PRO and cortisol data will be collected.*

23.3. Aim 2: Feasibility of intervention delivery

Technical and logistical issues with VC technology, internet, and software will be recorded. Descriptive methods will summarize the proportion of sessions attended. *We anticipate >75% of VC-CBCS participants will attend >75% of sessions.*

23.4 Aim 3: Patient satisfaction and acceptability

Qualitative data from each exit focus groups will be obtained to help improve the structure and content of the future VC-CBCS and study methods. The Patient Acceptability/Satisfaction survey will be analyzed as an average for the 14 sessions.[6] Items on the group dynamics survey will be evaluated at both time points.[6,99,110,111] Reasons for drop out will be evaluated in both conditions. *We anticipate that patients will find the VC-CBCS highly acceptable and useful, as measured by the Patient Acceptability survey and information provided during the exit focus groups.* If 19 of the 24 VC-CBCS participants find the intervention acceptable (overall score ≥3.5 out of 5.0), the point and interval estimate will be 79% [95% CI: 61, 100].

23.5 Aim 4: Explore changes in patient outcomes, mediators and intervention targets, as well as temporal associations and strength of associations among variables in a preliminary conceptual model, to inform a future efficacy trial

For each outcome measured before, during and after the intervention, we will obtain estimates of specific mean changes, treatment effects, standard deviations, serial correlations, corresponding confidence intervals indicating levels of precision or standardized effect size estimates (Cohen's *d*) of change. We anticipate that mean changes will favor the VC-CBCS intervention relative to SC.

Various exploratory methods may be used to fully examine the data and generate hypotheses to be evaluated in a future RCT. We may explore the weekly repeated measures for intervention targets and potential mediators/intermediate outcomes to identify targets rated as strongest by patients, and to identify the timing and magnitude of changes in mediators/intermediate outcomes during the VC-CBCS. To better understand potential causal pathways and refine the conceptual model, we may explore temporal correlations among targets, mediators (intermediate/secondary outcomes) and primary patient-reported and clinical outcomes. For example, we may explore associations of mediators with intervention-induced changes in health status, physical and mental symptoms, salivary cortisol, ALT and AST. We will estimate mean $\log_{10}$ cortisol as a diurnal function of time of day and compute summary values such as the area under the curve (AUC), AUC minus ground, and cortisol awakening.

24 STUDY CONDUCT

This study will be conducted in accordance with federal and institutional guidelines (https://www.hhs.gov/ohrp/regulations-and-policy/regulations/finalized-revisions-common-rule/index.html; (https://www.hhs.gov/ohrp/regulations-and-policy/regulations/finalized-revisions-common-rule/index.html) and relevant Good Clinical Practice (GCP) Guidelines described by the International Conference on Harmonization (ICH). The study will be conducted in compliance with this version of the study protocol. The protocol and any amendments will receive UNC Institutional Review Board (IRB) approval prior to initiation of the study. Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

We will apply all standard protections of patient confidentiality and data integrity during this study. Consent forms will be uploaded to REDCap and hard copies stored in a secure, locked location. All research data will be stored on a secure electronic server, behind a firewall at UNC, maintained and monitored by the UNC SOM ITS. Study documents will be stored in locked and secure file cabinets and on the CGIBD secure server in a folder accessible only to study staff. Audio-video files of the intervention will be uploaded to the CGIBD secure server to the private research folder.

25 DATABASE RETENTION

The REDCap database and all study-related materials will be maintained until all data are published and up to 5-7 years after the end of the study at UNC by the PI in collaboration with the NC TraCS Institute and SOM ITS. Hard copy data will be securely stored on the secure server and in locked cabinets. Access to electronic folders and REDCap will be terminated for staff no longer working on the project. Data initially stored on screened patients who were not enrolled will be deleted at the end of the study. If datasets are exported for analysis, no identifiers or contact information will be exported.

26 DATA AND SAFETY AND MONITORING PLAN

This study has a full DSMP that has been reviewed and approved by the NIH National Institute of Nursing Research (NINR) and is in accordance with the Policy of the NINR for Data and Safety Monitoring of Extramural Clinical Trials. Available in supplementary attachment. Study staff will adhere the guidelines in the DSMP.

26.1 Procedures for Adverse Events (from DSMPv2.0 - 27Sept2019)

In brief, we will identify, review, and report study-related serious adverse events (SAEs) according to UNC regulatory guidelines and OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events. The UNC IRB Standard Operating Procedures (dated: 6/2/2017) defines a reportable serious adverse events (SAE) as any event temporally associated with the subject's participation in research that meets any of the following criteria: 1) results in death, 2) is life threatening, 3) requires inpatient hospitalization or prolongation of existing hospitalization, 4) results in persistent or significant disability/incapacity, 5) results in congenital anomaly/birth defect, or 6) any other adverse event that, based on appropriate medical judgement, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above (UNC SOP 1401: 3.2.2.1.1). These SAEs will be reported immediately to the PI and Dr. Lechner, the Independent Safety Monitor (ISM), within 48 hours of notification. The PI and ISM will review the SAE and determine if the SAE is partially or fully related to study participation. (Note: We do not anticipate any study-related SAEs or AEs based on prior experience conducting these interventions and as this is a minimal risk behavioral intervention including no drugs, devices or procedures). Based on SAE review and ISM, the SAE outcome/conclusion will be recorded with study records. If the SAE is determined to be study-related, an ISM summary will be reported to the UNC IRB within 7 calendar days. If not study-related, it will be tracked but not reported. Unanticipated study-related AEs or problems will be reported within 14 days to the IRB. We will record SAEs and unanticipated study-related AEs in a regulatory binder. The NINR Program Officer will be notified of study-related SAEs or study-related unanticipated AEs within one month of reporting the event to the UNC IRB (per OHRP Guidance recommendations).

The target population has a higher prevalence of medical, psychiatric, and substance use disorders and conditions. Therefore, we anticipate learning about non-study related patient issues related to liver, cirrhosis, psychiatric, or substance use issues due to the natural history or these disorders and higher risk of these disorders in the target population. Under this protocol, the PI and ISM will not report non-study related events such as inpatient hospitalizations for medical conditions or symptoms (e.g., complaints of fatigue, nausea, pain) to the IRB or sponsor, although reports of these events will be tracked in a regulatory binder. We will follow a SOP to handle non-study related medical or psychiatric issues.

Dr. Evon will provide oversight and direct patient care commensurate with good clinical practice as a clinical psychologist and member of the UNC Liver Program. We do not anticipate any events that would halt accrual. If an event should occur, it would be discussed with ISM, staff and telemental health consultants. A review of eligibility criteria, patient monitoring, assessments, or the intervention may occur but is unlikely to halt accrual.

27 RESEARCH TEAM

NAME	DEPARTMENT NAME	ROLE
Donna Evon	UNC Department of Medicine	Principal Investigator
Michael Fried	UNC Department of Medicine	Co-Investigator
Susan Girdler	UNC Department of Psychiatry	Co-Investigator
Dawn Harrison	UNC Gastroenterology and Hepatology	Co-Investigator
Deborah Tate	UNC Department of Health Behavior and Department of Nutrition	Co-Investigator
Chip Bailey	Duke University School of Nursing	Co-Investigator
Suzanne Lechner	n/a Independent Contractor	Independent Safety Monitor

Cathryn Mainville	n/a Etheridge Private Practice	Group Facilitator
Leslie Morland	University of California, San Diego Department of Psychiatry Director, San Diego Regional Telemental Health Program, San Diego VA Health Care System	Telemental health Consultant
Jeremy Simpson	UNC School of Medicine Information Technology Security (ITS)	AV Support Engineer
Paul Stewart	UNC Department of Biostatistics	Biostatistician
Ashley Arrington	NC TraCS Institute, RCMU	Project Manager
Taylor Caron	Center for Gastrointestinal Biology and Disease	Research Coordinator
Ginny Sharpless	Center for Gastrointestinal Biology and Disease	Data Management Consultant

28 GLOSSARY OF TERMS

A1C – Hemoglobin A1C
AE- adverse event
ALT - alanine aminotransferase
AST - aspartate aminotransferase
BRFSS - Behavioral Risk Factor Surveillance System
CB – cognitive behavioral
CBCS - cognitive behavioral coping skills
CBSM – cognitive behavioral stress management
CBT – cognitive behavioral treatment
CGIBD- Center for Gastrointestinal Biology and Diseases
CTSA – clinical and translational science awards
CONSORT – Consolidated Standards for Reporting of Trials
DSMP – data safety monitoring plan
HCV- hepatitis C virus
HCV-PEG – Hepatitis C Virus Patient Engagement Group
HCV RNA – HCV RNA PCR test
IMB - informational-motivation-behavioral skills
IRB – Internal Review Board
MOCS - Measure of Current Status-Part A
NC TraCS- North Carolina Translational & Clinical Sciences Institute
NIH- National Institutes of Health
NINR – National Institute of Nursing Research
PRO- patient-reported outcomes
PROMIS- Patient Reported Outcomes Measurement System
PROP UP – patient reported outcomes project of HCV-TARGET
PSS – perceived stress scale
HRQOL- health-related quality of life
RCT - randomized controlled trial
REDCap - research electronic data capture system
SAE – serious adverse event
SAMISS - Substance Abuse and Mental Illness Brief Symptom Screener
SC – standard of care
SM – stress management
VC - videoconference

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