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Heart-Related Multiple Chronic Conditions in Primary Care: Behavioral Technology

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STUDY SUMMARY

Multiple chronic conditions (MCCs) are not simply aggregates of several individual conditions. They represent overlapping conditions that often have common root causes, and when grouped together can severely impact treatment options and quality of life for the patient. Primary care providers (PCPs) face many challenges in treating patients with MCCs. They need to help patients be motivated and informed enough to effectively manage their own conditions, but must balance that with the time demands of their practice. [1-5]

MCCs are common and expensive among patients aged ≥65 and are associated with lower quality of life, poorer response to treatment, worse medical and psychiatric outcomes, higher mortality, and higher costs of care. [7] Treatment of MCCs focuses on medical care, but patient self-management and loneliness matter too. Numerous studies indicate that chronic conditions contribute to loneliness and loneliness in turn contributes to reduced functionality and chronic illness. [11-13]

The primary purpose of this study is to conduct a randomized clinical trial (RCT) to examine the effects of C-CHESS--a web-based intervention--on health outcomes and healthcare use among older adults with 3 or all of the following 5 common, high-risk chronic conditions: hypertension, hyperlipidemia, diabetes, osteoarthritis and BMI of 30+. Patients in the experimental group will receive treatment as usual (TAU) plus C-CHESS. Patients in the comparison group will receive TAU+internet and links to helpful websites (e.g., NIH SeniorHealth). We assume that about half of participants will have their own computers and Internet access; we will give touchscreen laptops and provide Internet access to those who do not. The RCT will be conducted in primary care clinics that are part of the University of Wisconsin Department of Family Medicine's primary care network and the Medical University of South Carolina's Primary Care Clinics. The study will involve 330 patients age ≥65 who will be tracked for a total of 18 months--12 with access to the interventions and 6 months for follow up, with data collected every 6 months.

The C-CHESS Intervention

For the patient, C-CHESS (or ElderTree, as it will be known to participants) provides tools, motivation, and social support to help them manage their specific set of chronic conditions and communicate with peers and their PCP.

For the clinic, C-CHESS has a Clinician Report (CR), a visual dashboard of health-tracking data that can be customized based on the needs of the clinic. The CR provides alerts to the clinician when a patient passes a certain threshold. The dashboard is intended to help clinicians prepare for patient office visits.

BACKGROUND & SIGNIFICANCE

MCCs are common and expensive among patients aged ≥65. Among Medicare beneficiaries, 65% have 3 or more MCCs[8] and 23% have 5 or more MCCs. People with MCCs account for 90% of Medicare spending.[9] Per-capita Medicare expenditures increased with the number of chronic conditions from $211/year for beneficiaries with no chronic conditions to $13,973/year for those with 4 or more.[8] Among Medicare beneficiaries in 2010, hypertension (high blood pressure) and hyperlipidemia (high cholesterol) were the 2 most common chronic conditions, affecting 58% and 45% respectively; diabetes affected 28% and arthritis 29%.[22]

Treatment of MCCs focuses on medical care, not patient self-management. Most PCPs focus on managing medication and lab results for MCCs and less on strategies and skills for self-management. [10] However, treatment adherence, health tracking, and feedback to clinicians are important for patients with MCCs, given the challenges of polypharmacy and multiple ongoing treatment needs. Additionally, patients need education about how to live with their conditions, given that they are chronic.

The principles of self-management and support are well documented and relate to an array of health behaviors. [14-17] C-CHESS focuses on improving 1) patients' self-management, 2) patients' social

engagement and support, and 3) clinicians' case management (we use *clinician* to refer to physicians, nurse practitioners, and physician assistants).

Studies show that information and communication technologies can improve self-management and healthcare effectiveness. Recent reviews[18,19] found positive outcomes in 29 of 32 studies of chronic condition interventions delivered via computer and cellphone, with more impact coming from multi-service programs.[20] Our intervention will offer an array of services that can be tailored to each patient's multiple needs and is designed to increase the efficiency and effectiveness of clinic-patient interactions.

The Center for Health Enhancement Systems Studies (CHESS). CHESS is a research center at the University of Wisconsin–Madison. Over the past 30 years, CHESS has acquired an international reputation for developing and applying innovative applications of systems engineering principles and communication sciences to healthcare, specifically in interactive healthcare technology for patients, their family members, and providers. We have extensively studied what it takes to successfully implement these technologies within an organization. CHESS research projects are grounded in the belief that technology has the potential to transform and improve individual lives as well as the healthcare field.

CHESS researchers and programmers work with patients, family members, and clinicians to create web and smartphone applications that help individuals cope with health crises or medical concerns. To date, CHESS has created systems for a variety of health conditions, such as breast, colon, and lung cancer; asthma; aging; and addiction.

CHESS has a suite of evolving eHealth web and smartphone based innovations built on the principles of continuing care and self-management: long duration[26]; assertive outreach[27]; tracking[28]; prompts[29]; action planning[30]; problem solving[10]; self-tailoring[10]; peer, family, and care coordination.[33] In randomized clinical trials, previous CHESS innovations significantly improved: 1) asthma control for young children (mediated by relatedness)[18]; 2) quality of life and cost of care in HIV patients[35]; 3) quality of life and self-efficacy in breast cancer patients, including elderly women[36]; 4) risky drinking[39] ; and 5) symptom distress and length of survival in lung cancer patients (mediated by competence).[67]

Preliminary data

Most clinical trials of CHESS applications have examined its impact on a single chronic condition. One current study, Elder Tree CHESS, targets outcomes and a population similar to those in this study. Elder Tree CHESS is a web site that was developed as part of an AHRQ Center of Excellence in Active Aging grant to help adults 65 and older remain independent, primarily by reducing loneliness. C-CHESS will have as its base the services and design of Elder Tree, but will add new user features and information related to the target chronic conditions as well as a Clinician Report for medical staff.

Elder Tree was tested in an RCT involving 399 older adults from 3 Wisconsin counties (urban, rural, and suburban). We followed participants for 18 months and assessed outcomes at 0, 6, 12, and 18 months.[41]

Elder Tree subjects were asked to identify their chronic conditions so we could examine data about the impact of Elder Tree on those with MCCs. We identified 66 older adults with at least 3 of the 4 target MCCs. Subjects' conditions included (in addition to hypertension, hyperlipidemia, diabetes, and arthritis) cancer, pain, depression, anxiety, heart disease, obesity, osteoporosis, and falls. The Elder Tree RCT included 4 measures we plan to use in this study: health-related quality of life, use of primary care services, relatedness (feeling connected with others), and number of symptoms. For the clusters we propose to study in this project, we found moderate (0.4+) to large effect sizes, all favoring Elder Tree, with 2 exceptions in which small effects favored Elder Tree. These data helped us conduct power analyses and estimate sample sizes for the C-CHESS RCT.

Effect sizes from Elder Tree data					
Chronic Condition Clusters	*n* Control/ Elder Tree	Quality of Life	Fewer Primary Care Visits	Relatedness	Fewer Symptoms
Hypertension/hyper-lipidemia/arthritis	17/21	0.20	0.61	0.56	0.56
Hypertension/hyper-lipidemia/diabetes	11/10	0.40	0.66	0.36	0.45
Hypertension/arthritis/diabetes	16/11	0.96	0.71	0.52	0.53
Hyperlipidemia/arthritis/diabetes	14/14	1.09	0.56	0.91	0.75

As mentioned above, C-CHESS will add to Elder Tree the Clinician Report (CR), which alerts clinicians when thresholds are reached in a patient's status. We used a similar system in a lung cancer RCT comparing CHESS to CHESS+CR. The addition of the CR to CHESS improved ($p < .001$) symptom distress by over 100% (26.2% improvement with CHESS vs. 53% in those with CHESS+CR; n = 71 vs. 68 respectively). These statistics are averaged across 6 observations over 12 months. We expect the proposed CR to increase the effects of C-CHESS compared with Elder Tree.

Innovation: The intervention is innovative for the following reasons.

1. *Single disease ➡ Multiple diseases*. Information and communication technologies have shown promise in managing chronic conditions. But most address a single condition without addressing co-occurring issues. In contrast, C-CHESS will offer information for specific conditions as well as tools designed to improve behaviors that underlie MCCs generally, such as weight management. Patients will select behaviors they want to address. C-CHESS will be designed to help any combination of MCCs.
2. *Single intervention ➡ Multiple interventions*.[23,24] Many healthcare apps rely on one tool (e.g., texting), though different people with similar objectives may benefit from different tools. C-CHESS will offer a variety of options for online training and support.
3. *Complex ➡ Simple.* Many computer-based systems make extensive use of text and are complicated to navigate. Additionally, systems on smartphones are often challenging for older adults because vision problems and tremors make it difficult to use the small keys. C-CHESS will improve ease of use by offering large screens, voice and text options, and simple content.
4. *Clinic-based and periodic ➡ Sustained tracking and just-in-time clinician alerts*. Tracking and support for patients with MCCs usually consist of periodic, onsite contact with PCPs, who may be unaware of and/or cannot respond promptly to changes. Moreover, many patients avoid "bothering the doctor," foreclosing a source of help that might make a difference. C-CHESS will encourage patients to report symptoms daily, weekly, and monthly, depending on a patient's specific conditions and choice. When changes warrant just-in-time alerts, they will be automatically sent in a manner that minimizes clinician burden.
5. *C-CHESS will address loneliness.* Loneliness worsens chronic conditions. C-CHESS will address this by giving participants the power to give and receive social support.

The C-CHESS intervention

C-CHESS provides tools, motivation, and social support to help patients set, prioritize, track, and accomplish goals for managing their specific set of chronic conditions. C-CHESS is consistent with self-determination theory, which asserts that satisfying 3 fundamental psychological needs contributes to adaptive functioning: competence (feeling effective rather than overwhelmed), social relatedness (feeling connected to others), and feeling internally motivated (rather than coerced).[43]

The following describes key C-CHESS behavioral services:

- Cognitive behavioral therapy (CBT) life skills summaries: Behavior change, problem solving, decision-making, managing stress and fatigue,[44] and resolving communication problems via skills such as cognitive reframing, analyzing your behavior chain, and attentive listening.
- Goal setting and reminders: Helps patients set behavioral goals and reminds them of treatment plan activities (e.g., exercise), upcoming appointments, events of interest, skills, online relaxation exercises, peer support, and distracting activities. Patients will be asked if they intend to meet certain self-determined goals because this has been shown to improve adherence.[45]
- Treatment plan manager: Helps patients set priorities and reminds them to take medications and follow their treatment plan using schedules entered at setup and altered periodically as needed.
- Tracking, triage, and feedback: C-CHESS collects information about how a patient is feeling using patient-reported responses to prompts and provides links to relevant resources. Also sends inspirational messages and congratulations for patients' achieving their goals.
- Ask an Expert: Allows patients to anonymously seek advice about managing their MCCs.
- Tips and texts. Ideas on how to manage MCCs and their interactions.[42] Patients and clinicians can add to or comment on tips, web links (e.g., AARP drug interaction checker[46]), and other information.

Social engagement services provide:
- Social interaction options: Patients with MCCs give and receive support via emails, texts, and monitored online discussion groups. Past research consistently indicates that participating in social interaction via CHESS is associated with better health outcomes (e.g., quality of life, emotional well being).[47,48]
- Private messages: Enables C-CHESS members to communicate privately with other C-CHESS members. Along with discussion groups, private messages are one of the most popular services in current CHESS systems.
- Healthy Events: Suggests local activities that patients can add to their calendars according to guidelines established during setup.

C-CHESS's autonomy support tools provide:
- Thought for the Day provides motivational reminders of the importance of maintaining or improving health.
- Relaxation services: Games, recordings to guide progressive relaxation, deep breathing, and mindfulness.
- Personal stories: Audio/video accounts (based on interviews with MCC patients) focusing on care experiences (e.g., what patients would do differently, how they coped, tips they used).

C-CHESS Clinician Report (CR). MCCs can lead to rapid declines in health.[8] The CR can share timely information on patient general indicators (e.g., fatigue, mood, nutrition, sleep). C-CHESS will help clinicians prepare for patient office visits.

1.0 STUDY OBJECTIVES

This projects will test the use of an eHealth intervention called C-CHESS, to modify health behaviors and improve health outcomes in older adults with comorbid chronic diseases and health conditions.
Aim 1 Refine C-CHESS, using feedback from patients and primary care clinicians.
Aim 2 Conduct a randomized clinical trial to test 4 hypotheses:
1. *Primary outcomes:* Patients assigned to TAU+C-CHESS will have better quality of life and less primary care use (fewer visits) than those assigned to TAU+Internet.
2. *Secondary outcomes:* Patients assigned to TAU+C-CHESS will have improved composite scores; improved individual condition outcomes (mm Hg for hypertension, mg/dL for hyperlipidemia (LDL), HbA1c for diabetes, and pain for arthritis); and fewer symptoms from a list than patients assigned to TAU+Internet.
3. *Mediators:* Patients assigned to TAU+C-CHESS will have, compared with patients assigned to TAU+Internet, greater adherence to medications and appointments as well as improved competence,

relatedness, and autonomy.

4. *Moderators:* Improvements in primary outcomes for TAU+C-CHESS vs. TAU+Internet will be greater for women than men, those ≥ 75 vs. 65 to 74, and those with 3-5 chronic conditions vs. 6+.

Aim 3 Analyze data from the RCT and publish results.

Exploratory questions:

- Does C-CHESS reach a large proportion of targeted patients, get a large proportion of targeted clinicians to use CCHESS, get a large proportion of patients to regularly use CCHESS, and maintain that performance over time)?
- Does the use of specific C-CHESS services affect outcomes?
- Does the use of C-CHESS affect other health service use?

Primary Aim

Patients assigned to TAU+C-CHESS will have better quality of life and fewer primary care visits than those assigned to TAU+Internet.

C-CHESS will contain the Clinician Report to make it easier for PCPs to respond to important patient changes, pilot data suggested that primary care visits could be reduced. Reducing the number of primary care visits will both lessen provider burden and ultimately reduce healthcare costs.

Secondary Aim

Patients assigned to TAU+C-CHESS will have improved composite scores; improved individual condition outcomes (mm Hg for hypertension, mg/dL for hyperlipidemia (LDL), HbA1c for diabetes, and pain for arthritis); and fewer symptoms from a list than patients assigned to TAU+Internet.

A composite measure will combine Z scores of outcomes for each of the targeted chronic conditions, but because the composite score has not been validated and to help interpret results, we will also report results for each condition. Our pilot data showed positive effects for almost all combinations of conditions, and previous research (on breast[38] and lung[40] cancer; asthma[34]; HIV[35]; and alcoholism[39]) has shown that CHESS programs improve outcomes for individual chronic conditions. In addition, an extensive review of mHealth apps for cardiovascular disease[59] found promising results of mHealth in RCTs on hypertension and hyperlipidemia. Few of the programs for diabetes have been rigorously tested and reported.[60] We chose pain as the outcome for arthritis because Internet-based interventions have proven effective in reducing pain.[64]

Study Coordination

The UW-Madison Center for Health Enhancement Systems Studies (CHESS) is the coordinating site for this study. The UW study coordinator will oversee all recruitment activities which includes:

- developing recruitment and data collection processes that meet study objectives;
- training staff on protocol procedures prior to start of recruitment and continuous monitoring to assure compliance with the protocol and human subjects regulation;
- communicating with clinic site staff as needed via conference calls to monitor progress, inform of protocol changes/distribute new version of protocol, and address unanticipated issues or challenges;
- and manage all study data.

2.0 SELECTION OF SUBJECTS

Patient Recruitment: We will recruit 330 patients age ≥65.

Patients are eligible for the study if they:

1) are ≥65 years old
2) have been treated in the clinic for at least the previous 18 months with no plans to leave during the study period

3) have ≥3 of the following chronic conditions:
   - Hypertension
   - Hyperlipidemia
   - Diabetes
   - Arthritis
   - BMI ≥30
   - Chronic Kidney disease
   - Chronic pain
   - COPD
   - Congestive heart failure
   - Arrhythmia/atrial fibrillation
4) report no current psychotic disorder that would prevent participation
5) have no acute medical problem requiring immediate hospitalization
6) do not have a visual or motor impairment that prevents them from using a computer
7) be able to read and sign the consent form in English
8) have no known terminal illness;
9) be willing to share health-related study data and
   - Systolic and diastolic BP
   - Weight
   - BMI
   - HDL/LDL
   - HbA1C
   - pain score
   - health care utilization: hospitalizations (admission and discharge), number of ER visits, urgent care visits, PC visits, specialty care visits, long-term care visits, and rehab visits
10) allow researchers to share information with their primary care physician

We will document and describe eligible people who choose not to participate.

Clinician Recruitment: 15 providers (salaried, credentialed staff) from 5 different clinic sites will be identified and recruited to complete 3 qualitative interviews each over the course of the study. Site staff will be identified by the clinic and contacted by the UW study coordinator. Details of the study and their participation will be explained and if they agree informed consent will be collected. Staff are eligible for the study if they:

- Allow monitoring of their C-CHESS usage
- Are willing to participate in 3 interviews to share information about technology use at their clinic and feedback related to C-CHESS.
- Have a patient participating in the intervention arm of this study

3.0 REGISTRATION PROCEDURES

Patient Recruitment

In January of 2018, research staff will begin recruiting. The trial will involve 330 patients age 65 and older, randomized into two groups:

1. Patients in the experimental group will receive treatment as usual TAU + laptop + Internet access + C-CHESS
2. Patients in the control group will receive TAU + laptop + Internet access

Patient recruitment will be conducted in primary care clinics within the University of Wisconsin's Department of Family Medicine and General Internal Medicine, as well the Medical University of South Carolina.

School of Medicine and Public Health/MUSC employees will identify from clinic records patients who meet inclusion criteria.

The UW Clinical Research Data Service (CRDS) will extract the following data to determine patient eligibility per the eligibility criteria above. The data will be sent to the UW Office of Clinical Trials via REDCap or other secure method.

- First and last name
- Address
- Birth date
- Age
- UW Clinic Location
- Primary Care Doctor
- Has ≥3 of the following chronic conditions:
  - Hypertension
  - Hyperlipidemia
  - Diabetes
  - Arthritis
  - BMI ≥30
  - Chronic Kidney disease
  - Chronic pain
  - COPD
  - Congestive heart failure
  - Arrhythmia/atrial fibrillation
- # of chronic conditions
- Don't need an interpreter
- # of primary care visits in the last 18 months

Potential UW Health participants will either receive an opt-in letter from the UW Office of Clinical Trials or be recruited in-person at a scheduled clinic appointment. In the latter case, clinic staff or the Office of Clinical Trials will alert research staff when a potential participant has an upcoming clinic appointment. Staff will be available at the clinic on the specified date/time to conduct the enrollment visit if the patient agrees to speak with them.

Potential MUSC participants will receive an opt-in letter or MyChart message sent by the MUSC Biomedical Information Specialist. The message will describe the study and have a postage paid return letter inviting further contact from the UW study team.

Only MUSC, the UW Office of Clinical Trials, or SMPH Family Medicine staff will receive the list of potential subjects, process the mailings or MyChart messages, or identify upcoming clinic appointments.

UW study staff will call potential participants who opt-in to provide a detailed study overview including the benefits and potential risks of participation. If the patient is interested in participating, they will be asked questions to determine final eligibility: 1) do they have any acute medical problem requiring immediate inpatient treatment, 2) are they willing to allow their health care provider to supply lab data to the study team, or 3) are they willing to allow the study team to share high level information (graph that charts weekly scores related to the quality of your sleeping, nutrition, physical activity, memory, falls, moods, balance, pain, medication adherence and quality time spent with others, 4) do they have any plans to change health care providers in the next 18 months.

Patients who verbally confirm they want to be in the study and meet the screening criteria will be mailed the baseline survey and will receive a home visit where written consent will be obtained, the completed baseline collected, randomization determined, equipment set up, and training delivered. The baseline survey is expected to take 20-30 minutes to complete and will assess demographics, quality of life, symptom management, pain, medication adherence, and health care utilization.

Patients who consent to participate in-person at a clinic appointment will provide signed consent, be given the baseline survey, and a home visit will be scheduled to complete the activities described above.

Minority Recruitment Advisors

In addition to the general recruitment procedures described above, beginning in October 2019 three individuals active in the black community in Madison, WI will serve as advisors to the research team. They will provide feedback on recruitment materials, recruitment process, and ElderTree content and design which will inform future projects.

Patient Consent

Patients must agree to allow monitoring of their C-CHESS use and agree to allow their clinic to supply the study team with health care utilization and EHR related data, specifically lab scores for systolic and diastolic BP, weight, BMI, HDL/LDL, HbA1C, and pain. (as applicable to the patient), and diagnoses of anxiety, depression, osteoporosis, and cancer. The patient will be given the right not to share specific information and will retain the right to revoke their permission at any point.

The research team will always have a member available during standard operating hours for participants to contact with questions or issues. If a patient declines to participate, a research team member will determine reasons for non-participation so we can examine how patients who opt out differ from those who choose to participate.

The consent process will inform potential subjects of:

(1) the nature and purpose of the study

(2) the types of data that will be collected quarterly from the EHR (by the CRDS) and, for participants in the experimental group, from C-CHESS

- Systolic and diastolic BP
- Weight
- BMI
- HDL/LDL
- HbA1C
- pain score
- health care utilization: hospitalizations (admission and discharge), number of ER visits, urgent care visits, PC visits, specialty care visits, long-term care visits, and rehab visits
- osteoporosis
- cancer

(3) for participants in the experimental group, the types of data that will be shared with their primary care physician (a graph that charts weekly scores related to the quality of your sleeping, nutrition, physical activity, memory, falls, moods, balance, pain, medication adherence and quality time spent with others.)

(4) study risks and measures taken to mitigate

(5) their right to leave the study at any time

(6) the timeline of the study

Consent will be documented by obtaining a signed, IRB-approved consent forms from participants. Signed forms and other study data will be stored in a locked cabinet at the Center for Health Enhancement Systems Studies at the UW. After receipt of the signed consent forms, patients who need them will be issued their computer by research staff. Research staff will train patients on Internet safety and security and how to use the intervention. Research staff will help participants assigned to the experimental group choose a unique login name and password for C-CHESS. Subjects will be asked to use the intervention weekly.

Participants who do not already own a computer will be receiving a laptop as part of the study. The laptop has an administration interface that allows our technical team to access devices remotely if a participant calls tech support or reports a problem. If a participant loses their laptop or installs something that is causing problems, we have the ability to remotely wipe the device, lock it down, restore the operating system and/or run a security check. We can also do security updates remotely to make sure patches are up to date on each laptop and security software has not been disabled by the user.

Patient Randomization: Once informed consent and baseline measures have been obtained from patients, they will be randomized to either the experimental (TAU + C-CHESS) or control (TAU + Internet) group, stratified on gender, clinic site, and number of chronic conditions (3-5 vs. 6+). Patients who are in the experimental group will be further randomized into two groups, one will be asked to identify a health outcome to track and share with their physician using the Clinician Report and the other group will not.

When baseline assessment and consent are complete, the researcher will enter the participant number and randomization data into a randomization spreadsheet. The interviewing researcher, once informed of group assignment, will provide setup and training.

The research staff will train participants to use C-CHESS and customize it (e.g. by health condition) during a home visit. Participants will be asked to check in regularly, initially at a daily rate with frequency of at least weekly over the course of the study.

Patient Qualitative: Data will be gathered via an interview at 3 times from 6 patients at each of the 5 clinics (N=30). Each interview is expected to take 30-60 minutes and will take place either in-person at a place of the subjects choosing or via phone.

Recruitment: Participants will be identified through a consent form opt-in question and demographics as reported on the baseline survey. We will seek a mix of genders and number of chronic conditions. We will also look at C-CHESS use data to find a mix of users and non-users. We will contact potential participants by messaging them through the C-CHESS application or phoning them.

At setup and training, qualitative data will be gathered by the study team through observing training sessions with the participants. Participants will be asked to engage in think-aloud procedures during training to provide insights into their initial reactions and difficulties.

The think aloud instructions would be: “I’m going to talk you through the system. You’re in the driving seat, and you’re going to do all the button pressing and clicking. But it would be really great if you can talk out loud about what’s going through your head as you’re doing it. Anything at all. You like something, you don’t like something, you can’t tell what to do, you don’t know where to click, or you can’t read it… whatever you think. Don’t hesitate to say stuff that you don’t like or that’s confusing. We

have broad shoulders, and it's really important for us to learn from you.

The trainer might tell them to turn on the computer, then click on the ElderTree icon, and then type in a user name. The patient will be asked to give a running commentary as they try to do these things. They may say, for example, that they're not sure if they've pressed the button hard enough and are wondering whether to press it again, or that they're not sure which part of the screen they need to touch to get the type-in section for their user name. They can also comment on things they find interesting or intriguing. The point of this is not to categorize patients, but to identify training, instructions or site design issues that might need correction or adaptation.

At 6 months, half of the identified qualitative patient participants (n=15) will be interviewed either in-person or via phone using a standard survey. At12 months, the end of intervention period, the other half will be interviewed. Those who agree to meet in person (vs. talk on the phone) will be asked to show how they log in and navigate C-CHESS. Patients will be asked about barriers to use and perceived challenges and benefits of C-CHESS. At 6 months post-intervention, all will be re-interviewed about their experiences post-C-CHESS, including any ongoing effects of the intervention.

Patient Focus groups: Data will be gathered from 2 groups each with 3-7 unique participants who are or were enrolled in the experimental group. The focus group will take place in-person in a private meeting room at a public facility easily reached by participants (public library meeting room, senior center meeting room etc.).

Recruitment: Participants will be identified through consent form opt-in and demographics as reported on the baseline survey. We will seek mix of genders and number of chronic conditions. We will contact potential participants by messaging them through the C-CHESS application or phoning them.

During the focus groups participants will be asked about community and environmental barriers to fulfilling their personal goals, their thoughts on the intervention, and their thoughts on improving the system and using it to remove barriers. The focus group will take about 2 hours. Participants will be paid $50 for attending.

Across all UW-Health sites:

SMPH researchers are responsible for:

- Pulling participant lab data and transmitting to the study team
- Identifying potential subjects and relaying that information to UW Office of Clinical Trials

UW Office of Clinical Trials staff are responsible for:

- Sending an opt-in letter to potential subjects
- Communicating any patient contacts to SMPH

UW researchers are responsible for:

- Calling patients who have opted-in to explain the survey and receive verbal consent
- Administering the baseline and written consent
- Setting up the intervention

Across all MUSC recruitment sites, MUSC research staff are responsible for:

- Pulling participant lab data and transmitting to the study team
- Identifying potential subjects and relaying that information to MUSC Office of Clinical Trials
- Sending an opt-in letter or MyChart message to potential subjects
- Calling patients to explain the survey and receive verbal consent

- Administering the baseline and written consent
- Setting up the intervention

Across all recruitment sites, UW researchers are responsible for:

- Follow-up surveys
- Participant technical support
- Qualitative interviews with clinic staff and participants
- Data management

Clinician Recruitment and Consent:
In February of 2018, research staff will begin recruiting clinicians to conduct qualitative interviews with. This will involve a total of 15 total clinicians chosen from at least 5 different clinic sites. There will be no randomization, all clinicians will be part of the same study group.

To recruit clinicians, we will ask the participating clinics to identify individuals at the clinic who are serving patient participants and provide their name and email addresses. The study coordinator will contact them via email to see if they are willing to talk with us.

To be eligible for the study, clinicians must:

- Allow monitoring of their C-CHESS usage
- Be willing to participate in 3 interviews to share information about technology use at their clinic and feedback related to C-CHESS.
- Have a patient participating in the study

If the clinician is willing, details of the study and their participation will be explained via a follow-up phone call or email. If they agree informed consent will be collected. The consent process will inform clinician subjects of:

(1) the nature and purpose of the study

(2) study risks and measures taken to mitigate

(3) their right to leave the study at any time

(4) the timeline of the study

Qualitative interviews will be conducted with 15 clinic staff 3 times over the course of the study (to include one management person, one primary care doc, one nurse or nurse practitioner). Interviews will be done via phone or in-person at a location of the clinician's choosing. Interviews will be done at baseline, 12 months and 6 months post-test period.

In the baseline period, clinicians will be asked about anticipated barriers to participation and concerns about navigating C-CHESS and incorporating it into their treatment plans. Near the end of a clinic's intervention period, clinicians will be asked about factors that influenced their use of C-CHESS, perceptions of short- and long-term effects, and ways in which similar clinics might implement and sustain C-CHESS. In the post-test period, clinicians will be asked about enduring effects observed and implications of losing C-CHESS for treating their patients. Surveys should take about 15 minutes to complete.

5.0 TREATMENT PLAN

Treatment as Usual (TAU). Both the C-CHESS and Internet interventions will be paired with the patient's current care in process at their clinics. The UW and MUSC clinics each have one system for all

locations, so certain aspects of care at each site will remain constant, e.g., the use of 1 EHR and billing system.

The C-CHESS intervention. Participants in the C-CHESS group who need computers will receive a laptop and Internet access. They will be given log-in privileges to the C-CHESS website (the intervention) where they will access to tools, motivation, and social support for managing their specific set of chronic conditions.

When patient subjects use C-CHESS they will be prompted to complete weekly check-ins. They will be asked how they are doing specifically about sleep, nutrition, physical activity, memory, falls, moods, balance, pain, medication adherence and level of social interactions. These questions will be sent weekly on the C-CHESS system and will take about 2-4 minutes to complete. All questions are voluntary. Patients are free to refuse to answer any questions they are uncomfortable with. However, by answering the weekly questions C-CHESS can direct the patient to information on the site to help them in an area they are struggling. In addition, a graph will be created based on their responses and shared with the primary care physician via a physician log-in to the C-CHESS program (*Clinician Report (CR))*. This information is being collected and shared via the *Clinician Report* to allow clinicians to be better informed and provide treatment more responsively based on their patients' needs as they deal with serious health issues. All patients will be reminded that they are under no obligation to participate in this study, can withdraw from the study at any time, and in no way will their health care be affected by their participation in this study.

The Internet intervention. Participants in the comparison group who need computers will receive a similar laptop and Internet access as those in the experimental arm. Comparison-group subjects will receive training on how to use the Internet, if desired. Four general health information websites will be placed on the desktop of patients in the comparison group so the sites are easily accessible: the CDC website, FamilyDoctor.org (American Academy of Family Physicians), HealthFinder (DHS), and NIH SeniorHealth. The Medical Library Association recommends these sites.

Data collection

Participants will be tracked for a total of 18 months; 12 months with access to the interventions and 6 months for follow up. Data will be collected from: electronic health records (EHR), participant surveys (at months 0, 6, 12, and 18), and C-CHESS data.

Participant EHR data will be shared by SMPH or MUSC with the study team via RedCap. An employee designee of each site will retrieve from files or receive a passworded spreadsheet of participant study id via either encrypted email or Box.

Each participant survey is expected to take 20-30 minutes and will assess: demographic, quality of life, resilience, pain, medication adherence, and health care utilization. Surveys will be mailed to participants with a stamped return envelope included.

Participants will be paid $10 for each completed survey.

Survey data will be entered into REDCap (Research Electronic Data Capture). The UW study coordinators conducting surveys will be blind as to group assignment.

Qualitative participant data will be gathered via interviews with 30 participants conducted 3 times per person over the course of the study. Each interview is expected to take about 30-60 minutes and will take place either in-person or via phone.

Participant focus group data will be gathered 2 times during the study and will be used for system and content enhancement and improving the user interface. Focus groups will contain 3-7 unique participants, will last 1-2 hours and will be conducted in-person.

Use data. C-CHESS use data will be collected in time-stamped log files, including when a patient accessed C-CHESS, service(s) used, duration of use, pages viewed, messages posted vs. received, and the content of messages.

Staff subjects. Clinical staff will be consulted in the design and implementation of the Clinician Report (CR) feature of the website. They will also be asked as the study progresses about how they are using the CR, what they find helpful, and their opinions about the sustainability of C-CHESS in their organization. These discussions will be informal and participation is optional.

Unanticipated Events

Should any unanticipated problems arise the UW research team will work with the HS IRB to immediately address the problem, using the following guide:

What Event is Reported	When is Event Reported	By Whom is Event Reported	To Whom is Event Reported
Participant suicide as confirmed by a medical professional	Within 7 calendar days of initial receipt of information	Investigators	Internal IRB Internal DMC
Fatal or life-threatening unexpected, suspected serious adverse reactions	Within 7 calendar days of initial receipt of information	Investigator	Internal IRBs NHLBI and/or DMC
		Sponsor or designee[1]	FDA (if IND study)
Non-fatal, non-life-threatening unexpected, suspected serious adverse reactions	Within 15 calendar days of initial receipt of information	Investigator	Internal IRBs/ Institutional Officials NHLBI and/or DMC
		Sponsor or designee	FDA All participating investigators
Unanticipated adverse device effects	Within 10 working days of investigator first learning of effect	Investigator	Internal IRBs NHLBI and/or DMC
		Sponsor or designee	FDA (if IDE study)
Unanticipated Problem that is not an SAE	Within 14 days of the investigator becoming aware of the problem	Investigator	Internal IRBs/Institutional Officials, NHLBI and/or DMC
All Unanticipated Problems[2]	Within 30 days of the IRB's receipt of the report of the UP from the investigator.	IRB	OHRP
		Investigator[3]	Internal IRBs and DMC

Inappropriate use of the application

It is anticipated that the website may sometimes be used inappropriately. A research staff member will review and delete any messages deemed inappropriate (i.e nudity, threats, racism, bigotry). A research staff member will then follow up with the author of the inappropriate content. Discussion group guidelines have been developed and will be reviewed with participants as part of training.

Reasons for removing a subject from study

Cases in which a subject has ongoing borderline behavior will be evaluated individually and the subject may be removed from study if we feel it is in the best interest of the individual as well as the others on study.

Privacy and Confidentiality

To mitigate the risk of patient breaches of confidentiality, all subjects will be assigned a code number. A list of subject code numbers will be maintained by the UW project director and stored in a password-protected spreadsheet. This data will be kept in a secure, limited access server maintained by the College of Engineering.

Patient data will be identified using a unique C-CHESS ID number that will be aligned to the EHR Patient ID at each clinic. This approach allows a provider at a clinic to see the combined study and EHR data for a given patient, while members of the research team would see research data only. Investigators will have no record of client identity for analysis purposes. The Clinician Report is equipped with a log that records who accessed what data, at what time, and for how long.

Study data will be kept in a secure, limited access server maintained by the College of Engineering for analysis. The database administrator will grant password-protected accounts to provide access to study data at appropriate levels for various members of the research team. Members of the research team will be able to view de-identified individual and clinic-level aggregations of variables in the patient RTC.

When all study activities are complete identifiable information will be destroyed. De-identified study data will be stored on the secure servers for potential future unspecified research for which new IRB submissions will be initiated.

Potential Risks

The principal risks to participants are

- The potential for subjects to receive and act on bad information or misinterpret accurate information. To mitigate the risk of providing inaccurate or harmful information to patients, all C-CHESS content will be screened by Drs. Mahoney and Brown. C-CHESS information will be presented in text and audio formats that are easy to understand and accessible by individuals who have low literacy skills to reduce the risk of misinterpretation. Additionally, messages exchanged within the C-CHESS discussion groups will be monitored to make sure the information is accurate and that study participants are using the system for its intended purpose.
- There is a risk that information provided in C-CHESS will be used to the detriment of the subjects. Patients will be asked to set up a passcode on the laptop to protect their information in the event someone else finds it. All participants will receive information and guidelines on Internet safety and security during initial training.
- There could be a breach of confidentiality that could result in disclosure of research data outside of the study team. To prevent this, all subjects will be assigned a blind code number. These lists will be kept in a locked file in the CHESS office, and will not be shown to staff. Data collected from clinic records will have the name removed and a code number attached. Project staff who have access to the data will not have access to subject names. No clinic staff who have direct contact with the subjects will have access to data until the names are removed and the data is labeled with the blind code number. C-CHESS will automatically collect data on how often and for how long participants use the specific services within C-CHESS. This information will be collected by subjects' C-CHESS code number only and will not be attached to real names or identities.
- Internet service will be stopped after 12 months. Subjects may feel some loss when they no longer have this service. Participants will receive notice in advance of internet termination.
- Participants will be asked personal questions related to past or current behaviors and experiences, such as struggles with health issues, weight loss etc. that could produce anxiety, distress, embarrassment, or feelings of sadness.

- During study activities we may discover behavior that raises concern about elder abuse, harm to self or others. If we see anything that suggests that patient subjects or others face imminent risk of harm, we will contact appropriate others to intervene (e.g., State authorities, clinic, and/or police)

6.0 MEASUREMENT OF EFFECT

All scales being used in this study have good psychometric properties with similar populations. Listed below are the factors to be measured and measurement instruments with references to validation studies.

Quantitative analyses. Two types of analyses are planned: 1) a general, whole-sample analysis of outcomes not specific to any condition, and 2) analyses of condition-specific outcomes that permit integration across condition categories.

The first, general outcome category includes quality of life and primary care use which will be assessed with the same measures and same metrics regardless of conditions.

The second type of analysis is for condition-specific outcomes: mm Hg for hypertension, md/dL for hyperlipidemia, HbA1c for diabetes, and pain for arthritis. These outcomes will be analyzed in 2 ways. In one approach, scores on each measure will be transformed to Z scores and combined to create the composite score across all 5 outcomes, which will constitute an improper linear model with unit weighting; this is a secondary outcome. Thus, patients will be compared based on the pooled composite. Because we believe that change in the composite will reflect specific conditions and combinations, these factors will be entered as covariates in separate analyses to determine whether particular conditions or combinations of conditions are significantly related to the magnitude of treatment effects on the composite. Because patients often have more than 3 chronic conditions, we will code for the presence or absence of other common chronic conditions (e.g., cancer, pain, depression, anxiety, falls, heart disease, diabetes, and osteoporosis). The particular combinations involved will be entered as dummy variables. The second approach to the analyses of condition-specific outcomes will involve examining condition-specific outcomes individually, with only those individuals in the C-CHESS and comparison groups who have the pertinent diagnosis contributing data to the analysis (e.g., only those with diabetes will contribute data to the analyses involving HbA1c). The analytic approach to symptoms would be similar to the approach to the condition-specific tests. We will set a threshold for inclusion in the composite, and use as individual dependent variables the symptoms that occur in ≥10% of the sample.

This analysis plan should allow us to examine treatment-related change with regard to: 1) condition-specific clinical outcomes; 2) general outcomes reflecting disease coping and burden; and 3) condition-specific clinical outcomes when modeled as a composite score that reflects status with regard to the 5 major conditions.

Effectiveness of TAU+Internet vs. TAU+C-CHESS. We will use separate mixed-effects models to evaluate the primary and secondary outcomes. Each model will include fixed effects for TAU+Internet vs. TAU+C-CHESS, time (6, 12, and 18 months), and the arm-by-time interaction, including the baseline assessment of each outcome as a covariate. We will also determine whether clinic exerts main effects or interacts with the treatment condition. The latter will test the consistency of C-CHESS effects over different clinics and whether data can be pooled across sites. The initial intercepts will be modeled as random variables to estimate variance and covariance of intervention effects at the different fixed occasions, and across and between patients. These models account for dependence among successive observations made on the same patient and use all available data (not just complete cases). We will conduct treatment time contrasts between and within groups to test time-based effects, with our primary analysis focused on the C-CHESS effect at 12 months. Generalized linear mixed-effects models will be used for the count outcomes addressing primary care use. If a count outcome has sufficient variability, Poisson regression will be used; if not, the outcome will be coded as dichotomous (some service use vs. none) and logistic regression will be used.

Mediation. We will test 4 potential mediators of the intervention's effect on the primary and secondary outcomes. We will also test whether the condition-specific and composite secondary outcomes mediate the intervention's effect on the primary outcomes. Mediation will be tested by individually testing the 2 paths in the indirect effect and will conclude statistical significance only when the null hypothesis of no effect is rejected for both paths in the mediational pathway. To limit the number of analyses, we will use Bolt's approach[94] of first using a screening approach that examines only mediational models with outcomes and potential mediators significantly affected by the intervention. We will then use separate univariate models to determine which mediate the intervention effect on given outcomes. If 2 or 3 mediators are found, we will simultaneously enter all the significant mediators into the same model. If 4 mediators are found, we will enter the 'strongest' mediator first and then test whether adding remaining mediators shows significant mediational effects.

Moderation. A moderation model holds that the strength of the relation between intervention and outcomes is a function of the level of other variables and tries to explain under what conditions the treatment model functions. We will test whether gender, age (65-74 vs ≥75), and number of chronic conditions (3, 4, or 5) moderate the effect of the intervention on outcomes. Also, when standardized composites are used as the dependent variable, type of chronic condition will be used as a moderator to determine if the composite varies meaningfully by condition. Participants will list changes in chronic conditions at 6 and 12 months.

Moderated mediation. Although both constructs of mediation and moderation are of interest in our research, the process is more complex than just these factors. For example, a variable (e.g., relatedness) may act as a stronger mediator for 1 subgroup (e.g., women) than another (e.g., men).

Qualitative analyses. Through 3 interviews we will gather qualitative data from clinic staff to provide additional insights into their use of the CR.

In the baseline interview, clinicians will be asked about anticipated barriers to participation and concerns about navigating C-CHESS and incorporating it into their treatment plans. Near the end of a clinic's intervention period, clinicians will be asked about factors that influenced their use of C-CHESS, perceptions of short- and long-term effects, and ways in which similar clinics might implement and sustain C-CHESS. In the post-test period, clinicians will be asked about enduring effects observed and implications of losing C-CHESS for treating their patients.

Feedback from these interviews will be used anecdotally and will help the research team improve the design and delivery of the CR.

7.0 STUDY PARAMETERS

Patients will be randomized on a 1:1 ratio to TAU + internet or TAU+C-CHESS. Subjects will be stratified by gender, number of conditions and study site. It is anticipated that up to 330 patient subjects will be recruited at the participating clinics. Staff subjects will have access to C-CHESS for the duration of the study. Patient will have access to C-CHESS for 12 months.

8.0 STATISTICAL CONSIDERATIONS

Power analyses for primary and secondary outcomes. Our power analysis was based on Elder Tree pilot data and other studies that examined the impact of behavioral interventions on single chronic conditions.[95] A meta-analysis[96] of self-management interventions found significant effects on HbA1c for diabetics (d=-.36), and on systolic blood pressure among hypertensives (d=-.39). Other studies found a moderate effect size (d=.61) on pain behavior[97] and a small effect on number of primary care visits (d = .28) when patients attended self-management and peer-support meetings.[98,99]

Because effect sizes vary for interventions of chronic conditions, we want our expected effect sizes to be conservative and yet clinically meaningful. We therefore chose an effect size of d=.40 for our primary

outcomes (quality of life and primary care use) as well as individual condition measures (secondary outcomes) and the composite score based on them. Adequate power (1-β =.80, two-tailed α =.05) would require a final sample of N=200 patients (100 per arm).[100] Since we will examine 4 clusters, with 3 conditions per cluster, we will need 132 per arm. Assuming 20% attrition, we will recruit N=330 patients (33 per arm per clinic). This should also be sufficient for detecting similar effect sizes (at a power of 1-β =.80) for condition-specific changes in diabetes,[101] hypertension,[102] and arthritis.[103] The literature is less clear in hyperlipidemia but 50% of patients are non-adherent to statins,[104] and statins have a high effect size,[105] so our goal may be achievable.

Power for mediation and moderation analyses. Power for detecting parameter changes in the structural model was estimated using a procedure of Satorra and Saris[106] that approximates the non-central chi-square distribution. A total N of 220 patients will provide adequate power (> .80) to detect a group difference in a parameter by moderate .4 standard deviations. With an N of 264 in our primary analysis, we are confident our secondary analysis will have adequate power.

Impact on power calculations of adding attention control and the Clinician Report. We are using a placebo comparison group to remove the Hawthorne effect, not to contribute to managing chronic conditions. Conversely, the addition of the Clinician Report to the Elder Tree system upon which C-CHESS is based should have a positive effect. We compared CHESS to CHESS+CR in a lung cancer RCT and found statistically and practically significant improvement in symptom distress by adding the CR. Overall, we believe this change will make our power analyses conservative.

Missingness

In previous work, we completed 85% of interviews at 4, 8, and 12 months and kept missing data on core interview items to about 2%; we expect these rates in this study. In primary care, data are not likely to be missing at random (i.e., the probability that data are missing relates to what the data would have been had the data been observed). Because this may lead to biased parameter estimates for our models, we will identify missing data patterns and use pattern-mixture modeling to test the sensitivity of our longitudinal intervention analysis to missing data assumptions,[107,108] and conduct other sensitivity analyses after imputing missing data with a range of clinically plausible values based on explicit assumptions for the missing data (e.g., best-case, worst-case; with and without multiple imputation).[109,110]

9.0 RECORDS TO BE KEPT

- Subject Intake
- Subject Demographics
- Subject Consent Forms
- HIPAA Authorization Form
- Baseline and follow up survey data
- Coded C-CHESS use data
- Coded patient lab scores and health care utilization
- Coded transcripts from focus groups and interviews with patients
- Coded transcripts from interviews with clinic staff

Appendix A

CENTER FOR HEALTH ENHANCEMENT SYSTEMS STUDIES

Data Monitoring Committee (DMC)

For this project, the UW ICTR Data Monitoring Committee (DMC) will act as the Monitoring Board to oversee the study. The UW ICTR DMC is comprised of experienced members (core plus ad hoc) with expertise required to oversee this study. The DMC members will review protocol-specific reports created by statisticians using data pulled from the Research Electronic Data Capture (REDCap) data management tool. These standard reports will include an overview of study objectives, a review of actual and projected accrual rates, an evaluation of patient demographics for balance of randomization, and a summary of the number and seriousness of adverse events. An interim analysis of study results may be performed and source documents may be reviewed to allow the DMC to independently judge whether the overall integrity and conduct of the protocol remain acceptable based on data provided and reported by the Principal Investigator. This is a low risk study, but if we do conduct interim analyses our statistician will take into consideration the reduction in statistical power that will occur with each iteration. The DMC will make recommendations to the Principal Investigator that could include actions of continuation, modification, suspension, or termination.

The composition of the DMC contains experts qualified to review this protocol, including MDs in Pharmacy, Cardiology, Critical Care, and Psychiatry.

In providing oversight for the conduct of this study, the ICTR DMC will meet in-person annually during the 5-year study to review all adverse events. Additional meetings may be scheduled as determined by the DMC or as requested by the PI.

The predefined stopping points for this study will include excess rates of hospital re-admissions or quality of life determinates, exceeding 30% of pre-test values in both cases. We will submit all events, including both serious and non-serious adverse events and unanticipated problems, to the NHLBI, the DMC and the UW Health Sciences IRB in accordance with the following timeline:

What Event is Reported	When is Event Reported	By Whom is Event Reported	To Whom is Event Reported
Fatal or life-threatening unexpected, suspected serious adverse reactions	Within **7 calendar days** of initial receipt of information	Investigator	Internal IRBs NHLBI and/or DMC
		Sponsor or designee[1]	FDA (if IND study)
Non-fatal, non-life-threatening unexpected, suspected serious adverse reactions	Within **15 calendar days** of initial receipt of information	Investigator	Internal IRBs/ Institutional Officials NHLBI and/or DMC
		Sponsor or designee	FDA All participating investigators
Unanticipated adverse device effects	Within **10** working days of investigator first learning of effect	Investigator	Internal IRBs NHLBI and/or DMC
		Sponsor or designee	FDA (if IDE study)
Unanticipated Problem that is not an SAE	Within **14 days** of the investigator becoming aware of the problem	Investigator	Internal IRBs/Institutional Officials, NHLBI and/or DMC
All Unanticipated Problems[2]	Within **30 days** of the IRB's	IRB	OHRP

	receipt of the report of the UP from the investigator.	Investigator[3]	Internal IRBs and DMC

REDCap, a secure on-line data entry portal, will be used to standardize data capture between the multiple project sites. Project personnel at each study site will have the ability to enter data into REDCap via an individual user log-in. The user log-in can be configured to limit access to identifiable data, downloadable data sets, and data from other sites.

This Charter is for the Data Monitoring Committee (DMC) for the Center for Health Enhancement Systems Studies. The Charter will define the primary responsibilities of the DMC, its relationship with other trial components, its membership, and the purpose and timing of its meetings. The Charter will also provide the procedures for ensuring confidentiality and proper communication, the statistical monitoring guidelines to be implemented by the DMC, and an outline of the content of the reports that will be provided to the DMC.

UW Institute for Clinical and Translational Research
Data Monitoring Committee Charter (Update 8/11/2016)

1.1 INTRODUCTION

The UW Institute for Clinical and Translational Research (UW ICTR) has developed an organizational structure to provide the appropriate oversight and monitoring of clinical research to ensure the safety of participants and the validity and integrity of the data.[1]

To meet these needs, UW ICTR will convene a group of multidisciplinary experts to:

1. monitor subject safety and data integrity across the UW-Madison clinical research infrastructure, and
2. serve as the Data Monitoring Committee (DMC) for investigator-initiated clinical research protocols that require and request an independent DMC

The UW ICTR Data Monitoring Committee (ICTR DMC) covers responsibilities of entities often referred to as a Data and Safety Monitoring Committee (DSMC) or a Data and Safety Monitoring Board (DSMB).

The term "clinical research" is used throughout this document as defined by the National Institutes of Health (NIH). The NIH definition of clinical research is "(1) Patient Oriented Research: Research conducted with human subjects (or on material of human origin such as tissues, specimens and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Patient-oriented research includes: (a) mechanisms of human disease, (b) therapeutic interventions, (c) clinical trials, and (d) development of new technologies. (2) Epidemiologic and behavioral studies; (3) Outcomes research and health services research.[2]

Changes to this Charter may not be made without approval by the ICTR DMC. Protocol specific information should be included in an addendum or memorandum of understanding approved by the DMC.

2.1 SCOPE

To monitor participant safety across the infrastructure, the UW ICTR DMC will use the clinical research management software, ICTR OnCore or the research electronic data capture application, REDCap, to identify trends within and across the spectrum, including the incidence of serious adverse events (SAEs), subject accrual, and subject retention.

As noted, the UW ICTR DMC will provide data monitoring for individual clinical research protocols in need of DMC review (as determined by the Principal Investigator (PI), the funding agency, the local Scientific Review Committee, or the local Institutional Review Board (IRB), and for which no DMC exists). For these studies, the UW ICTR DMC will be the primary data and safety advisory group for the PI. The DMC will periodically review study results, evaluate the number and seriousness of adverse events, determine whether the basic protocol assumptions remain valid, judge whether the overall integrity and conduct of the protocol remain acceptable based on data provided and reported by PI, and make recommendations to the PI. Using the UW ICTR DMC will require the use of the clinical research management software, OnCore, licensed by UW ICTR to act as the data management tool for the protocol under review or the research electronic data capture application, REDCap.

DMC review will be based on the NIH[1] and U.S. Food and Drug Administration (FDA) guidelines.[3] Additional attention will be given to UW-Madison investigator-initiated protocols, with a focus on:

a. Protocols with high-risk subjects
b. Protocols with high-risk or novel interventions

c. Studies in special or vulnerable populations
d. Protocols with survival as the outcome measurement
e. Phase III and IV studies
f. Long duration/long-term studies
g. Protocols with an investigator held IND or IDE application

Protocols with a formal DMC review process, such as industry sponsored protocols and those being conducted under the purview of the UW Carbone Cancer Center Data and Safety Monitoring Committee, will be excluded from the ICTR DMC reviews.

In the course of reviewing local Serious Adverse Events (SAEs), the ICTR DMC may review protocols that are under the purview of an external DSMC or DSMB in order to monitor the trend of drug- or device-related SAEs across disparate protocols and sponsors.

3.1 ORGANIZATION

3.1 Composition of the DMC

ICTR DMC membership will consist of a core of multi-disciplinary members with experience in clinical research including, but not limited to, clinicians, scientists, and statisticians. In addition, an extensive list of ad hoc members will represent expertise to complement that of the core members and provide the flexibility to serve the diverse research landscape at UW.

3.2 Appointment of DMC Members

The DMC Co-Chairs and members (voting and non-voting) are appointed by the UW ICTR Director with input from ICTR Schools and Department Chairs as needed. The DMC core members will review all protocols under the purview of the committee.

DMC members will serve three years before rotating off the DMC, with staggered appointments to retain institutional experience. If a member is unable to continue participation on the DMC, the DMC chairs and members may recommend a replacement to the UW ICTR Director.

4.1 RESPONSIBILITIES AND FUNCTIONS

4.2 Responsibilities of ICTR DMC:

The ICTR DMC will function as the official DMC for an individual protocol, as requested by the study PI or other group, such as the IRB or Scientific Review Committees. The DMC may also identify and review trends within and across the infrastructure in need of independent review. Identification of trends will focus on the incidence of SAEs, subject accrual, and subject retention with effort to identify the areas where improvement can be made.

When performing its role as official DMC of an individual protocol, the ICTR DMC will request initial review of the protocol after Scientific Review Committee approval, and before subject enrollment has been initiated for the purposes of;

- Reviewing the study protocol and any protocol amendments and making recommendations to the PI.
- Reviewing overall data collection methods and safety monitoring procedures and recommending additions or adjustments.
- Assisting with the definition of safety and related parameters to be monitored, frequency of committee monitoring reviews, methods for review, and establishment of criteria for making recommendations to the PI.

4.3 Responsibilities of the Principal Investigator

The PI is responsible to the DMC for the following:

- Making resources available to the DMC as required to carry out its designated functions including use of ICTR OnCore clinical research management software or the research electronic data capture application, REDCap.
- Provide ICTR DMC relevant external information at the time of review (such as data from other protocols establishing unequivocal treatment benefit or harm, data from clinical practice indicating unsuspected and unacceptable treatment side effects, developments superseding current treatment, treatment withdrawal from the market)
- Communication of ICTR DMC actions and all pertinent regulatory information to the FDA, the local Scientific Review Committee, the local IRB, and the sponsoring agency when applicable.
- Adverse events (AEs) and severe adverse events (SAEs) will be reported to the DMC within the same time frame as required for reporting to the IRB.
- Submitting IRB-approved changes of protocol that affect the safety or primary outcome(s) to the ICTR DMC.

5.1 DATA MANAGEMENT RESPONSIBILITIES

ICTR OnCore or REDCap must be used as the data management tool for protocols utilizing the ICTR DMC for their protocols.

ICTR OnCore or REDCap will be used to;

- Electronically capture data needed to address study objective(s) and subject safety.
- Provide data sets containing all data necessary for creating DMC reports to the Data Management Center/Core or statistician assigned to the protocol.

The protocol Data Management Center/Core (if applicable), or PI, will be responsible for the following:

- Collection and on-site monitoring of case report forms.
- Ensuring the completeness and accuracy of all data collected to the extent required by the DMC.

6.0 RESPONSIBILITIES OF THE STATISTICAL DATA ANALYSIS CENTER OR DESIGNATED STUDY STATISTICIAN

The designated Statistical Data Analysis Center (SDAC) or designated study statistician is responsible for the overall data analysis preparation for review by the DMC, using templates and guidance provided by the ICTR DMC. When acting as an ICTR DMC for an individual protocol, review will occur annually, at a minimum. The frequency of ICTR DMC review will be determined by the PI and specified in the statistical plan of the protocol, including stopping rules.

The designated SDAC or designated study statistician prepares reports for review by the DMC based on data generated as part of the study and validated by the Data Management Center. The SDAC also prepares reports based on supporting documentation for events and may receive copies of case report forms directly from study participant care physicians for these events.

The SDAC will prepare interim reports that will include recruitment, baseline comparisons of risk factors, protocol compliance, primary and secondary outcomes, safety and adverse effects, and a limited number of sub-group analyses when relevant. The SDAC will repeat these analyses for the final analysis of the protocol.

7.1 CONDUCT OF DMC MEETINGS

7.2 Scheduled Meetings

7.2.1 Scheduled Meetings when serving as the DMC for the UW-Madison clinical research infrastructure.

When acting as an institution-wide DMC to monitor subject safety across the clinical research infrastructure, the ICTR DMC will convene in a single location at a minimum of once yearly, or more frequently as needed. If necessary, additional meetings may be held by conference calls if the DMC so decides.

7.2.2. Scheduled Meetings when serving as the DMC for investigator-initiated clinical research protocols that request an independent DMC.

When acting as a DMC for an individual protocol, the ICTR DMC will convene prior to initiation of the study to help define safety and related parameters to be monitored, frequency of committee monitoring reviews, methods for review, and a priori criteria for study discontinuation. A scheduled meeting will convene in a single location at a minimum of once yearly. However, the frequency of additional scheduled meetings depends on patient enrollment and safety event rates, thus frequency could be greater than once yearly. If necessary, additional meetings may be held by conference calls if the DMC so decides.

7.3 Meeting Format

7.3.1. Open/Closed Meetings
The ICTR DMC does not meet the definition of a "governmental body" as defined in sec. 19.82(1), Wis. Stats., in that it was not created by constitution, statute, ordinance, rule or order. As a result, the ICTR DMC does not operate consistent with the Wisconsin Open Meetings law. The use of the term "open session" herein describes that portion of a meeting in which the PI and/or his/her staff are invited to be present at the meeting.

The use of the term "closed session" herein describes that portion of the meeting when only the ICTR DMC members, staff from the SDAC, and invited guests (such as those with a particular needed expertise) are present at the meeting. Such terms should be not be given their meaning under the Wisconsin Open Meetings law.

7.3.2 Format of Meetings when serving as the DMC for the UW-Madison clinical research infrastructure.

When acting as an institution-wide DMC to monitor subject safety across the clinical research infrastructure, the ICTR DMC meetings will consist of only closed sessions. Attendance to these meetings will be restricted to ICTR DMC members and administrative staff, staff from the SDAC, and any invited guests. NHLBI staff representatives will be voted in and will be allowed to attend as invited guests.

7.3.3 Format of Meetings when serving as the DMC for investigator-initiated clinical research protocols.

ICTR DMC meetings will follow Robert's Rules of Order in all cases in which they are applicable and not inconsistent with ICTR DMC standard operating procedures. The meetings will consist of open and closed portions. During the initial open portion of a meeting, the PI and his/her designated staff may be invited to make brief presentations and be available for questions from and discussions with the DMC members without revealing interim data. The open session will only discuss aggregate data to reduce the risk of misleading conclusions. The closed session will be restricted to ICTR DMC members and administrative staff, staff from the SDAC, and any invited guests.[4] The closed session will discuss accumulating data by assigned and unblended treatment group.

7.3 Content of Review

During the closed session, members will review the DMC report prepared by the SDAC or protocol statistician. The report will include the following items;

a. Study progress (e.g. overall accrual, accrual rates)
b. Adverse events, especially serious adverse events
c. External information (such as data from other protocols establishing unequivocal treatment benefit or harm, data from clinical practice indicating unsuspected and unacceptable treatment side effects, developments superseding current treatment, treatment withdrawal from the market)
d. Interim Data Analysis (if applicable)
e. Data Quality; to potentially address data quality, the ICTR DMC reserves the right to review the data, accompanying source documentation, or other relevant study data materials, if requested.
f. Impact of findings on the risk-benefit ratio

7.4 Recommended Actions

In either DMC function – infrastructure reviews or acting as an individual protocol's DMC – the committee will recommend one of the following actions to the study principal investigator:

a. The protocol can continue without change
b. The protocol or protocol plan should be modified. Modifications may include, but are not limited to, changes in inclusion/exclusion criteria, frequency of visits or safety monitoring, alterations in study procedures, adjustments in sample size, changes in duration of observation and follow up.
c. The protocol should be suspended, allowing subject visits to occur as scheduled to monitor subject safety, but not allowing new subjects to be enrolled until ICTR DMC concerns have been appropriately addressed.
d. The protocol should be discontinued, or one treatment arm of the protocol should be discontinued, (with provision for orderly discontinuation) due to:
    i. Serious concerns about subject safety
    ii. Serious concerns about the safety of interventions
    iii. Benefits do not outweigh the risks to subjects
    iv. Protocol outcomes do not justify risk
    v. New developments impact subject safety/ethics
    vi. Unreasonable degree of difficulty of procedures

Authority for continuing, modifying, suspending, or termination of the protocol is the responsibility of the PI, IRB, FDA, or other regulatory authority. The ICTR DMC provides independent recommendations.

Correspondence, to include the date of DMC review, and the committee recommended action, will be shared with PI of the study in question.

7.5 Quorum

A quorum consists of a simple majority (51%) of ICTR DMC members present at the scheduled or unscheduled meeting or participating by phone.

7.6 Voting

To vote, a Committee member must be present at convened scheduled meetings, unscheduled meetings, or be a participant through conference calls. For voting purposes, a simple majority of the quorum is required to pass a proposal or motion. The chair of the meeting does not vote. A member may abstain from voting, but their presence at the meeting still counts towards quorum. A member may also recuse themselves due to a conflict of interest, which will lower the quorum. On a tie vote the proposal, motion, or recommendation fails. Additional discussion and a new proposal, motion, or recommendation may be made.

If quorum cannot be achieved, a sub-committee may convene to make recommended actions to the study team. The sub-committee must include at least 3 ICTR DMC members consisting of a chair, statistician and member with medical expertise. In this instance unanimity must be achieved to pass the recommendation to the study team. The recommended action will be considered for formal approval at the next DMC meeting at which a quorum is reached. If unanimity is not achieved the review will be deferred to the next meeting.

7.7 Procedures for Sharing Recommended Actions with the Principal Investigator

Duly voted and passed DMC recommended actions will be transmitted in writing to the PI within seven working days of the meeting at which the recommended action was passed. The PI has the responsibility to forward the unedited letter detailing recommended actions and all pertinent regulatory information to the FDA, the local Scientific Review Committee, the local IRB, other site IRBs, the sponsoring agency, or other oversight bodies when applicable and pertinent.

The PI also has the responsibility of responding to the DMC's recommended actions within 10 working days from the date on the DMC letter. If the recommended action is termination or suspension due to a safety issue, the PI must respond within 2 working days of receiving the DMC letter.

7.8 Review Notification and Meeting Minutes

Meeting minutes are prepared by DMC administrative staff with the DMC Chair for each DMC meeting, distributed in a timely manner after each meeting, and reviewed and approved at the subsequent meeting.

With the expectation that the PI may be masked to study treatments, and that the meeting minutes may contain some data by treatment groups (even if the treatments are designated by code), the meeting minutes will not be forwarded to the PI.

Instead, the PI will receive notification that the protocol was reviewed; the date of the review, and the committee recommended actions that were passed. This notification will be forwarded to the PI with instructions to share the notification with appropriate local and federal oversight bodies.

At the end of the study and after treatment is unblinded, a copy of the meeting minutes will be forwarded to the PI with recommendations to forward to appropriate local and federal oversight bodies.

Correspondence, to include the date of DMC review and the committee recommended action, will be shared with the local IRB, in addition to the PI of the study in question.

7.9 Confidentiality

All members will treat as confidential the reports, meeting discussions, summary notes and minutes. Each member will sign a Confidentiality Non-Disclosure Agreement that will accompany documentation that entails their responsibilities as a DMC member. All ad hoc members, invited guests, and SDAC staff will also sign a Confidentiality Non- Disclosure Agreement.

7.10 Financial Conflict of Interest Guidelines (when acting as a DMC for an individual Protocol)

When performing its role as official DMC for an individual protocol, a DMC member has a conflict of interest if on the protocol under review he or she, or his/her spouse, domestic partner or dependents:

a. serves as PI, co-investigator, key personnel, or likely author on publications resulting from the protocol under review (the DMC may waive this requirement as needed);
b. is involved in monitoring, analysis, or evaluation of subjects on the protocol under review;
c. is in a position that gives him or her the ability to influence the conduct of the protocol in any role other than that of a DMC member;[4]
d. has any intellectual property or financial conflict of interest with the protocol under review.

Additionally, a DMC member has a conflict of interest if he or she, or his/her spouse, domestic partner or dependents, buys, sells, or holds stock options with the Sponsor of a protocol under review for the following periods: from the first meeting at which the DMC reviews the protocol until the last meeting at which the protocol is reviewed and the study results are made public.

A DMC committee member also has a conflict of interest if he or she, or his/her spouse, domestic partner or dependents, serves as a paid consultant to the Sponsor during these same periods. The guidelines also apply to staff at the SDAC. The ICTR DMC will hold, and update annually, conflict-of-interest statements from each member.

Certain other activities are not viewed as constituting conflicts of interest but must be reported annually to the DMC chair. These include: the participation of a member in educational activities supported by the Sponsor, the participation of members in other research projects supported by the Sponsor, and occasional scientific consulting to the Sponsor on issues not related to the product in the protocol and for which there is no financial payment or other compensation.

Committee members and SDAC staff who have a conflict of interest may answer DMC member questions, but must remove themselves during sensitive discussions and recuse themselves from voting on the protocol in which they have a conflict, unless the DMC (absent the member or staff person with a conflict of interest) determines that these guidelines should be waived.

An ICTR DMC member may be from the same department or research program as the PI whose protocol is under review, if none of the above referenced conflict of interest criteria are present.

ICTR DMC will strive to minimize potential perceived conflict of interest, thus may invite ad hoc members from nearby institutions outside the UW when their area of expertise is needed.

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