Technology-based **C**omprehensive Cardiac Rehabilitation **T**herapy (TaCT) for women with cardiovascular disease in a middle-income setting: A randomized controlled trial protocol

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ABSTRACT

Women are under-represented in cardiac rehabilitation (CR) despite the benefits, and this is exacerbated in lower-resource settings where CR is insufficiently available. In this randomized controlled trial, the effectiveness of the Technology-based Comprehensive Cardiac Rehabilitation Therapy (TaCT) eCR intervention on functional capacity, risk factors, quality of life, heart-health behaviors, symptoms, and morbidity will be tested among women with CVD in a middle-income country. Following a pilot study, a single-centre, single-blinded, 2 parallel-arm (1:1 SNOSE) superiority trial comparing an eCR intervention (TaCT) to usual care, with assessments pre-intervention and at three and six months will be undertaken. One hundred adult women will be recruited. Permuted block (size 10) randomization will be applied. The 6-month intervention comprises an app, website, SMS texts with generic heart-health management advice, and bi-weekly 1:1 telephone calls with a nurse trainee. Individualized exercise prescriptions will be developed based on an Incremental Shuttle Walk Test (primary outcome) and dietary plans based on 24-hour dietary recall. A yoga/relaxation video will be provided via WhatsApp, along with tobacco cessation support and a moderated group chat. At 3 months, intervention engagement and acceptability will be assessed. Analyses will be conducted based on intent-to-treat. If results of this novel trial of women-focused eCR in a middle-income country demonstrate clinically-significant increases in functional capacity, this could represent an important development for the field considering this would be an important outcome for women and would translate to lower mortality.

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1. Background:

Cardiovascular diseases (CVD) are among the leading burdens of disease worldwide (Gallagher et al., 2017), with an even higher burden in low and middle-income countries [LMICs] (Peiris et al., 2021). Thus, many are living chronically with CVD, putting them at increased risk of morbidity and mortality (Jernberg et al., 2015), which is also costly for society and health systems (Gheorghe et al., 2018). In the LMIC of India, for instance, the prevalence of CVDs is estimated to be 54.5 million (Abdul-Aziz et al., 2019), and access to care is limited (Fullman et al., 2018).

Cardiac Rehabilitation (CR) is an established and guideline-recommended (Babu, et al., 2020; Smith et al., 2011) model of care comprehensively delivering secondary prevention strategies (Grace et al., 2016) demonstrated to reduce mortality and morbidity (Dibben et al., 2021; Kabboul et al., 2018), as well as resulting in clinically-meaningful benefits in functional capacity, risk factor reduction, and quality of life (QoL) in LMICs (Babu et al., 2016, 2020; Madan et al., 2014; Mamataz et al., 2022). To date, a recent systematic review revealed there have been only five trials of CR in India (Mamataz et al., 2022) (Babu et al., 2011; Eraballi et al., 2018; Eraballi et al., 2018; Jena et al., 2020; Raghuram et al., 2014; Venkatesh et al., 2019; Yadav et al., 2015).

CR is traditionally delivered in a supervised setting (Ghisi et al., 2022), which leads to capacity constraints and patient barriers to access, resulting in under-utilization (Grace et al., 2021). For instance, in India (Babu, et al., 2020), there is only 1 CR "spot" for every 160 incident ischemic heart disease patients per year (Turk-Adawi et al., 2019), such that the unmet need for CR in India is over 3 million "spots" per year - the greatest of any country in the world (Pesah et al., 2019). Accordingly, remote models of CR have been developed (Thomas et al., 2019), which are shown to be of equivalent benefit to supervised models (Anderson et al., 2017). Importantly, remote models are safe (Stefanakis et al., 2022) and

may also be more cost-effective (Frederix et al., 2017), which is key in LMICs. Technology-based CR, where information and communication technologies are applied to deliver the components (Chong et al., 2021), has been integral with the onset of the COVID-19 pandemic (Babu et al., 2020; Ghisi et al., 2021). Several meta-analyses also demonstrate the benefits of technology-based CR for patient outcomes, including through mobile phones [i.e., eCR] (Chong et al., 2021; Jin et al., 2019; Ramachandran et al., 2021; Rawstorn et al., 2016). These models of CR are well-accepted by patients (Subedi et al., 2020) where access to technology is good (Gallagher et al., 2017), such as in India (Jain et al., 2019). Interestingly however, while three of the five CR randomized controlled trials (RCTs) in India were "hybrid" such that patients transitioned from supervised to remote delivery (Mamataz et al., 2022), there has been no trial assessing eCR in India, and indeed only two trials in any LMIC that used smartphones (Dorje et al., 2019; Passaglia et al., 2020).

CR is greatly under-utilized overall when compared to other secondary prevention recommendations (Virani et al., 2015), but there are subgroups of patients who are even less likely to access these proven programs (Resurrección et al., 2019). In particular, women are significantly less likely to participate in CR (Samayoa et al., 2014), which is particularly concerning given their greater need (Kawamoto et al., 2016; Mauvais-Jarvis et al., 2020; McSweeney et al., 2016), given they have greater social and economic disadvantage than men, are often diagnosed at more advanced stages of disease, are treated less aggressively, have more adverse effects from treatment and often have poorer outcomes than men (Vogel et al., 2021). Accordingly they may benefit to a greater degree than men (de Souza e Silva et al., 2021; Ekblom et al., 2021). Women's CR barriers have been extensively studied, and include lack of transportation / distance, depression / anxiety, lack of support / encouragement, comorbidities, and associated concern over pain or fatigue during exercise, as well as time conflicts due to their multiple role obligations (Grace et al., 2009; Supervia et

al., 2017). It has been suggested that CR tailored to women and offered remotely could address these barriers (Ghisi et al., 2022).

There are 28 studies of women-focused CR, including 11 RCTs, of which two were in LMICs [China and Iran] (Mamataz et al., 2021). Five of the RCTs used some form of technology (i.e., phone calls, cassette tapes, app), including the two from LMICs, which used phone calls (Feizi et al., 2012; Tsai et al., 2019). Therefore, we endeavoured to: (1) develop a comprehensive eCR model (Technology-based Comprehensive Cardiac Rehabilitation Therapy; TaCT) tailored to women in India, (2) pilot test and assess acceptability, and (3) assess effectiveness on functional capacity (primary outcome), in addition to risk factors (blood pressure, lipids, waist circumference), QoL, heart-health behaviours, symptoms (e.g., syncope, angina, anxiety), and morbidity. We hypothesize that TaCT will be acceptable and result in significantly better outcomes when compared to usual care.

2. METHODS

This is a single-centre, single-blinded, 2 parallel-arm (1:1 allocation concealed) superiority RCT comparing an eCR intervention (TaCT) to usual care in a middle-income country, with assessments at: (1) baseline, (2) three months, and (3) six months (corresponding to the end of intervention; Fig 1).

2.1. Setting

The study will be conducted in the outpatient department of cardiology in a private tertiary care referral centre, Kasturba Hospital, in Manipal, Udupi District, Karnataka state, India. The centre performs both percutaneous and surgical revascularization. Patients are referred to the hospital by the general physicians in the catchment area, as well as from other districts of the state; In addition to this, some patients visit the department of their own accord or receive follow-up care following acute treatment.

Volumes are approximately 185 patients per day, of which 50-60 are female.

Outpatient care (i.e., patient registration and specialty consultation charges, and also the cost of tests [e.g., bloodwork, treadmill tests, electro- and echocardiograms] and medicines) is either covered by health insurance or, most commonly, patients pay out-of-pocket (including for any CR).

2.2. Participants

The inclusion criteria are: women over the age of 18, who possess and can independently use a smartphone (or there is one in the home owned by another family member that can be used). They must be able to read and communicate in Kannada and/or in English, and not knowingly going to be inaccessible during the period of study. With regard to cardiac condition, only stable CVD patients (i.e., no on-going chest pain, and with left ventricular ejection fraction >40%) who have been diagnosed for at least one month are eligible. The CVD must be attributable to myocardial atherosclerosis / ischemia and /or hypertension (e.g., post-myocardial infarction, coronary revascularization).

With regard to exclusion criteria, patients with other cardiac conditions such as congenital, rheumatic, cardiomyopathies or arrhythmias; comorbid peripheral or cerebrovascular diseases, which limits their exercise; or other health conditions which limit their ability to participate in CR (e.g., advanced cancer, neurological conditions, respiratory disease, serious mental illness [e.g., severe depression], sensory impairments, musculoskeletal issues) will not be eligible for the trial.

2.2.1. Sample size calculation

The sample size was calculated based on a previous trial with the same primary outcome, as well as similar design and setting (Chaves et al., 2019). We powered for a clinically-significant change in the primary outcome of Incremental Shuttle Walk Test (ISWT) distance in meters from pre to post-test. The sample size for the study was calculated using the standard deviation 121.6m and minimum-clinically important difference of 75.6m

(Eq 1). The following assumptions were made: 5% significance level; 80% power to detect a difference between groups; and random assignment to the two groups in equal proportions. Expected loss to follow-up was 15%.

We rounded up for the ease of block randomization, such that we aim to recruit 50 women per arm (i.e., 100 women total). However, the sample size for the study will be re-considered after the pilot study.

Eq 1. Formula used to calculate the sample size

$$n = \frac{2\sigma^2(Z_{1-\alpha/2}+Z_{1-\beta})^2}{D^2}$$

2.3. Sequence generation, allocation concealment, and randomization

Permuted block randomization with equal block size will be used for the study; There will be 5 blocks, with a block size of 10 participants. An external member who is not directly involved in the study and is blind to the purpose of the trial will generate the sequence by using computer-generated random numbers (www.randomizer.org). Allocation will be concealed by using sequentially-numbered, opaque and sealed envelopes (SNOSEs).

2.4. Data Collection Procedures

Consecutive women visiting the outpatient cardiology department will be screened for eligibility by the first author (HJM). A participant information sheet will be provided, and written informed consent will be sought. Where voluntarily provided, baseline data will be collected from all participants (self-report and chart extraction) and the ISWT will be undertaken. Then randomization will occur.

Participants will be followed up at three months with surveys delivered via phone and at six months for surveys and physical assessment when they visit the outpatient cardiology department for their regularly-scheduled visits. The primary outcome will be assessed by a

trained physiotherapist blinded to the trial objectives and allocation. The surveys will be provided to the patients by the investigator (HJM) to be completed independently. If any patients miss their 6-month follow-up visit, responses for the self-reported measures will be obtained through the telephone.

Data will be entered by participant identification number only into SPSS by HJM. Double data entry will be undertaken, and 10% of the data will be randomly checked for any errors in entry. Randomized arm will only be merged into the data set after all follow-up data and cleaning are complete.

2.5. Trial Arms

2.5.1. Development and Nature of the TaCT intervention

The aim of the 6-month TaCT outpatient, technology-based phase II CR intervention is to support female patients to make heart-healthy lifestyle changes (i.e., nutrition, exercise, stress management, tobacco cessation, medication adherence) and to manage their health (i.e., the health risks of blood pressure, lipids, central obesity) to reduce their risk of further cardiovascular events, in line with secondary prevention recommendations (Visseren et al., 2021). The intervention is developed in the context of the existing CR program, to support intervention sustainability and scale. It will be offered at no charge to participants. There are no in-person sessions after the initial assessment, except the final assessment at 6 months.

The intervention was designed to be women-focused, building on other such CR models (all in higher-resource settings and generally not using technology) (Mamataz et al., 2021). The intervention is delivered virtually by a female provider and is technology-based, hence accessible to women who more often have time-related barriers due to household and family obligations and travel-related barriers (Grace et al., 2009). Given women's greater psychosocial needs (Shanmugasegaram et al., 2012), several features were incorporated: (1) peer support via moderated WhatsApp chat (app commonly used by the target population),

(2) provision of yoga and meditation video for stress management, and (3) discussion of psychosocial concerns as part of bi-weekly (fortnightly) phone calls. In the phone calls, women are also asked about any unique education needs. Finally, women will be supported to exercise in their preferred mode, with their exercise prescription tailored according to their comorbidities and function.

2.5.2. TaCT Delivery Modalities / Communication with Patients

TaCT materials are provided in Kannada, with some also in English. The technologies used for delivering TaCT are (Fig 2): (1) a mobile phone-based App developed for the trial called "Sukhi Hrudaya" (i.e., Healthy Heart), (2) website (with information about the intervention and generic CVD patient education materials to support lifestyle changes; https://www.sukhihrudaya.in/), (3) Short Message Services (SMS) texts (bulk messages), (4) WhatsApp (e.g., basic food guide, yoga/meditation, group chat), and (5) bi-weekly telephone calls (behaviour change promotion, risk factor management), all offered from time of recruitment through the 6 month intervention. The only part of the intervention that is synchronous is the initial session and the bi-weekly phone calls.

Though there are many existing health Apps and other technologies available on the market, recent literature reviews (Jin et al., 2019; Meddar et al., 2022; Rawstorn et al., 2016) reveal there are no comprehensive apps covering all core CR components, tailored to low-resource settings and to women (Sengupta et al., 2020). The TaCT CR App is developed with the users in mind, who have minimal education and experience using interactive technology. The TaCT app will be downloaded to participant's phones from the Google Play store and the connection to the intervention will be added. At the same time WhatsApp will be downloaded and the intervention website will be bookmarked. Participants will be shown how to use the apps until they are comfortable. Participants will be asked to consult the calendar which appears on the app home page to check for the times of their biweekly calls. The app also

includes their individually-tailored current exercise prescription and dietary plan, their medications, whether their risk factors are at target, and what goals they should be working towards.

SMS messages will be sent through Probulk in English or Kannada (depending on patient preference), with sender name HRDAYA (i.e., "heart" in Kannada). Generic texts regarding lifestyle advice (exercise, medication adherence, diet) will be sent one to two times per week; These 30 texts are based on the Mobile4Heart trial (Elnaggar et al., 2021), with some slight modifications to ensure local relevance and some added to address health behaviours other than exercise. Individualized texts with dates for any tests or appointments during the intervention period will also be sent.

Several individualized TaCT features will also be delivered via WhatsApp. Individualized recommendations on diet and the diet plan (as well as tobacco cessation as applicable) will be sent to the patients through WhatsApp. This will be done by the first author (HJM), in consultation with applicable experts on the team.

Moreover, participants will be provided with a video for yoga (Pranayama) and meditation/relaxation, such that all core CR components are delivered (Grace et al., 2016). The video was prepared by the first author (HJM) in Kannada, with English sub-titles. It was then reviewed and approved by 3 clinicians (cardiology, women's health, nursing). An introduction to the practices precedes the demonstration. The link to the video will also be pushed to participants via WhatsApp. Finally, the first author will invite all intervention participants to an asynchronous group chat, which she will moderate.

Finally, the template for the bi-weekly phone calls is provided in Supplementary file 1. Any reported symptoms or queries from patients received through any of these means will be addressed; The first author (HJM) will consult the member of the team of the applicable discipline for advice on response.

2.5.3. TaCT Secondary Prevention Recommendations

Intervention content was developed initially in English by the first author (HJM) following a review of CR guidelines and online search of education materials (National Heart Foundation of Australia, 2019). Eleven experts then reviewed the materials to ensure they were evidence-based, culturally-relevant, and patient-centered (i.e., from the fields of Cardiology, Physiotherapy, Cardiovascular Technology, Medical-Surgical Nursing, Nutrition, and Psychology). The content was then translated to the regional official language of Karnataka state (Kannada) by the bilingual primary investigator (M.Sc Nursing, PhD Student, ICCPR CR Foundations Certification); this was again reviewed by bilingual experts.

While many of the secondary prevention recommendations are generic for all patients (Visseren et al., 2021) [e.g., stress management], individualized exercise and diet recommendations will be provided based on their functional capacity and 24-hour dietary recall. With regard to the former, based on the results of the functional capacity test, exercise will be prescribed at a moderate intensity using Borg's rating of perceived exertion (Borg, 1982) [i.e., 13] with exercise duration starting from 15-30 minutes, five days per week, in the mode of their choice (walking most frequent) (Moore & Kramer, 1996). Prescriptions will be generated upon consultation with the exercise specialist of the CR program. The exercise prescriptions will be progressed based on patient reports of their activity (frequency, intensity, time), perceived exertion levels, and discussion of symptoms on the bi-weekly phone calls (fortnightly). Women will be encouraged to work up to 150 minutes of moderate-to-vigorous intensity physical activity per week, as is safe (Squires et al., 2018). Resistance exercise for the upper body using items available at home (e.g., bottles of water), and lower body, using body weight, will be incorporated into the exercise program.

To assess dietary intake in order to provide a customized diet plan for participants, a 24-hour recall will be used (Chawla & Arif, 2013). This captures detailed information about

all foods and beverages consumed by the respondent in the past 24 hours (from midnight to midnight the previous day). Responses will be entered into Dietcal (Indian nutrition software) to determine deviations from dietary recommendations of the Indian Council of Medical Research recommended dietary allowances (*Dietary Guidelines for Indians - A Manual*, 2011). These deviations will serve as the focus for individualized WhatsApp messages and will be discussed on the biweekly calls. Moreover, dietary recall results along with clinical status will be used to recommend one of six diet plans developed for the study (3 each for patients with or without comorbid diabetes, at 1600, 1800 or 2000kCal/day) on the basis of body mass index and heart-healthy diet requirement; the diet plan will be shared with participants via WhatsApp and in the app. Generic advice regarding weight, and heart-healthy eating is provided via SMS. Information is also available on the website.

Participants are asked in the baseline survey if they have difficulty paying for medication and whether they have insurance coverage (Chowdhury et al., 2022). For those who can afford medications, women will be asked on the phone calls about cardiac medication adherence in relation to those recommended in patient charts. Where there are issues, barriers will be discussed so strategies to overcome them can be suggested. Generic advice regarding medication adherence is provided in an SMS and on the website. Finally, tobacco users are connected to local cessation resources, and sent WhatsApp cessation messages.

2.5.4. Pilot Test

In a sample of 10 eligible consenting women, the TaCT intervention will be piloted for one month. Early after exposure to the app, participants will be asked via a 1-1 video call to navigate the app while thinking out loud (Eccles & Arsal, 2017). The purposes are (1) to determine whether the app is applicable and realistic for target women and whether it meets their information needs and offers an acceptable volume of content and (2) to receive input

on graphics / visuals and ways to promote their continued use of the app and how it could be revised to better meet their needs. The first author (HJM) will record the interview and analyze it for improvements that could be made.

In addition, each week, participants will be invited via WhatsApp to send any open-ended feedback regarding utility, challenges, unaddressed issues, and suggestions on how all elements of TaCT can be improved. Throughout the pilot, the first author will also notate any feasibility issues with regard to trial implementation itself such as recruitment, measurement, communication with patients (including content of queries from participants), and retention.

At the end of the month, participants will be asked to complete the 10-item System Usability Scale (Lewis, 2018; Brooke, 2013). We will assess intervention engagement, as outlined below.

2.5.5. Control arm

Participants in the control group will receive routine care provided at the hospital. Usual outpatient care is delivered by a cardiologist, supported by a multidisciplinary team of nurses, physiotherapists, and cardiovascular technicians for testing. The cardiologist prescribes patients medication, and for exercise and/or dietary advice, they may refer to the physiotherapy or nutrition / dietetics departments as applicable; patients must pay for these services and hence use is not common. Patients are usually scheduled for follow-up time visits at six months and one year, but this varies based on the patient's condition.
There is an inpatient and outpatient CR program at the hospital. CR is initiated in most inpatients (Satyamurthy et al., 2020). Generally, only inpatients with heart failure or pulmonary hypertension, limited mobility/ poor functional status, or with comorbidities such as diabetes or kidney disease are referred by their cardiologist to the outpatient CR program (i.e., patients who would be excluded from this trial). If the patient is referred and they enroll, a customised exercise prescription is given to the patients at moderate intensity based on

Borg's rating of perceived exertion (Borg, 1982; Williams, 2017), to follow at home. The CR program would be in touch with the patient via phone about a month later to further tailor the exercise program. There is no further education other than what is offered in inpatient CR. All participants are asked about any inpatient or outpatient CR participation upon enrollment into the trial. After the completion of the study, control participants will be directed to the intervention website for the patient information.

2.6. Measures

Participants will report sociodemographic (e.g., work status, education level, healthcare coverage including for medication) and clinical characteristics (e.g., menopausal status, any previous CR participation, age at first diagnosis, comorbidities). Some of the sociodemographic items from a CVD and gender measure were incorporated (e.g., hours in household labour per week, number of children) (Pelletier et al., 2015). Clinical information including medications will be extracted from charts. These variables are assessed via investigator-generated items (e.g., sociodemographic characteristics), validated self-report items or scales (e.g., exercise, diet), and objective clinical measures. All self-reported items were available in English or Kannada, and patients can elect their preferred language.

For the former and the self-report scales that were not validated in Kannada, the first author (HJM) drafted and translated the materials, which were then reviewed by a panel of experts including cardiologists, physiotherapists, epidemiologists, nurses, cardiovascular technicians, and dietitians, to review the content validity and terminology. The material was modified based on the suggestions given. Then, the modified measures were administered to 5 patients to assess the clarity of the items, their comprehensibility, and to identify any ambiguity in the terms. After modifications were made accordingly, the reliability of the translated scales was specifically assessed in 20 patients.

2.6.1. Primary Outcome – Functional Capacity

The Incremental Shuttle Walk Test (ISWT) is a valid and reliable test of functional capacity (Hanson et al., 2018; Lelis et al., 2019). The patient is directed to walk around two cones set 9 metres apart (so the final track is 10 metres) in time to a set of auditory beeps. Initially, the walking speed is very slow, but each minute the required walking speed progressively increases. The patient walks for as long as they can until they are either too breathless or can no longer keep up with the beeps, at which time the test ends. The number of shuttles are recorded (i.e., each time the patient reaches a cone is 1shuttle); Each shuttle represents a distance of ten metres. This will be assessed at baseline and 6 months in accordance with patient visits to the hospital. To mitigate anticipated loss to follow-up, the self-report Duke Activity Status Index (DASI) (Hanson et al., 2018; Hlatky et al., 1989; Shaw et al., 2006) will also be administered at all 3 assessment points. It is a 12-item self-report questionnaire for measuring functional capacity, which correlates with peak oxygen uptake. Each endorsed item is multiplied by a specific MET (Metabolic Equivalent of Tasks) weight.

2.6.2. Secondary Outcomes

Clinical risk factors of waist circumference and blood pressure will be assessed. Waist circumference (cm) will be assessed in accordance with the World Health Organization. Blood pressure will be assessed in accordance with best practices (Diagnosis & Assessment, 2020) using an automated device. These outcomes are only assessed at baseline and the final follow-up when patients come to the centre. Available lipid data will be extracted from the outpatient department records. The remaining self-report measures below will be administered at all 3 assessment points.

Quality of life will be assessed by the psychometrically-validated MacNew Instrument (Hofer et al., 2004; Hofer et al., 2016; Vecchis & Ariano, 2016), which has a validated Kannada version available (Höfer et al., 2004). It consists of 27 items, through

which a global score and 3 subscale (physical, emotional and social) scores are computed. Scores range from 1 to 7 for each, with a higher score indicating better QoL.

2.6.3. Heart-Health Behaviours

To assess physical activity, the Global Physical Activity Questionnaire (GPAQ) developed by the World Health Organization will be administered (Herrmann et al., 2013; WHO, 2021). It comprises 16 questions regarding physical activity participation in 3 settings/domains, as well as sedentary behaviour. The domains include work, active transport and recreational activities. Item responses are calculated to METS.

To assess dietary behaviour, a 24-hour dietary recall will be used (Chawla & Arif, 2013). This captures detailed information about all foods and beverages consumed by the respondent in the past 24 hours (from midnight to midnight the previous day). Three 24-hour dietary recalls will be taken comprising the diet of two weekdays and one weekend day. Estimates of food intake will be assessed using calibrated measuring cups to identify the quantity. The dietary intake of macronutrients and micronutrients will be compared with Recommended Dietary Allowance (RDA) of the Indian Council of Medical Research Expert Committee (*Dietary Guidelines for Indians - A Manual*, 2011) by the dietitians on the team.

Finally, other heart-health behaviours will also be assessed. Medication adherence and tobacco use will each be assessed by a single item from the International Council of Cardiovascular Prevention and Rehabilitation's International Cardiac Rehab Registry (ICRR) data dictionary (Chowdhury et al., 2022). Items were also generated by the investigative team regarding attending cardiac care appointments and generally following physician advice for managing their CVD.

2.6.4. Other Outcomes

Frequency of cardiac symptoms were assessed by a single item from ICRR's data

dictionary (Chowdhury et al., 2022). To assess the severity of anxiety symptoms, which are particularly common and hazardous in female heart patients (Denollet et al., 2009), the Generalized Anxiety Disorder [GAD-7] scale (GAD-7 English version) will be administered. Anxiety severity is calculated by assigning scores of 0 to 3 for each of the 7 items, to denote frequency of symptoms (e.g, 3 corresponds to "nearly every day"). Thus, GAD-7 total scores range from 0 to 21; Scores of 5, 10, and 15 represent cut-points for mild, moderate, and severe anxiety, respectively. The scale has been psychometrically validated against an independent structured psychiatric interview and is reliable (Spitzer et al., 2006). The Kannada translation of this tool is linguistically valid (GAD-7 Kannada version).

Morbidity will be assessed by a single item from ICRR's data dictionary (Chowdhury et al., 2022), and modified to capture other healthcare utilization relevant to this setting such as visits to physiotherapy or dietetics.

2.6.5. Intervention Fidelity, Engagement and Acceptability

Any issues in terms of intervention implementation will be documented, such as inability to reach a patient for a phone call, or failure to send a WhatsApp or text message. To assess intervention engagement, we will collate the number of times the participants opened the app, the number of "hits" on each page of the website, and the proportion of "read" WhatsApp messages and contributions to the group chat. Finally, acceptability will be measured by 24 items based on previous research and adapted for the purposes of this trial, on a 5-point Likert scale from "strongly disagree" to "strongly agree" (Weiner et al., 2017). These will be assessed at 3 and 6 months in intervention participants. Sample items include 'I will use the information in my daily life', 'the information was difficult to understand', and 'the CR intervention really met my needs as a woman with heart disease'. The investigative team developed the items and they were pilot tested in patients.

3. Statistical Analysis

First, to understand the generalizability of the data, response and consent rates will be computed. Age and type of cardiac condition will be summarized in the sample and compared to that of the outpatient department more broadly. Internal reliability of the validated scales translated to Kannada by our group will be computed (i.e., Cronbach's alpha).

SPSS version 25.0 and R 3.6.3 will be used to analyse the data. Descriptive statistics for participant characteristics will include (1) mean and standard deviation for normally-distributed data or median with interquartile range for skewed data, (2) frequency with percentages for categorical data. Besides sociodemographic data, inpatient or outpatient CR by arm will be summarized. Retention rate will be computed at the 3 and 6-month follow-up for the surveys and at 6 months for the ISWT. Baseline differences in sociodemographic and clinical characteristics as well as outcomes between those retained versus lost to follow-up at 6 months will be assessed using t-tests or chi-square as applicable.

Any issues with intervention implementation or fidelity as well as adverse events or harms observed will be collated. Engagement and acceptability will be described as detailed above.

All analyses will be conducted at an individual-level according to intention-to-treat principles. Missing outcome data will be imputed using appropriate techniques depending on whether it is at random (multiple imputation) or not at random (last observation carried forward or the mean of observations).

The effectiveness of the intervention will be reported as difference in proportions at 95% confidence interval and at 80% power. The comparisons will be done by applying appropriate statistical tests adjusting for the multiple comparison tests. Linear mixed model in R with the default options will be used to determine the intervention effect size considering

duration of follow-up and number of observations in the follow-up to study the effect of the intervention (independent variable) on each outcome (dependent variables).

4. Anticipated Limitations

The primary limitation of the trial is the inability to double-blind given the nature of the intervention. Measures have been put into place to ensure blind outcome assessment. Notable also will be limits to generalizability given the trial is single-centre. If results are favourable, broader testing would be warranted.

Difficulty of recruitment of women with CVD to trials is well-documented (Beckie et al., 2009). While participants will not be compensated for their time or participation, the intervention is designed in a way that no additional site visits are required, which is often a major obstacle to participation (e.g., distance, transportation, associated costs). Moreover, CR usually costs patients, but it is offered free through the trial. Penetrance of mobile phones is high in India, and the gender tailoring of the intervention should be of interest to women.

Retention is also a common issue in longitudinal behavioral trials. We are interested in intervention engagement. Participants who are not willing to come for their 6-month follow-up with their cardiologist in the outpatient department will be called to complete their assessments over the phone (although unfortunately this introduces bias as there will be no blinding in that instance). Moreover, given the primary outcome is an objective measure requiring a visit, we will administer a validated self-report measure of functional capacity (i.e., DASI) that can be also administered on the phone to secure as complete data as possible on all participants. Moreover, we have anticipated loss to follow-up in our sample size calculation, and have had very high retention in previous CR trials in LMICs (Chaves et al., 2019).

With regard to measurement, first, to achieve blinded outcome assessment, a different therapist will be performing follow-up ISWTs, which could introduce error. However, as the

ISWT is an externally-paced test, the variation between supervising therapists is negligible. Strict adherence to the standardised instructions provided by the developers further minimises any inter-observer bias (Singh et al., 1992). To be conservative however, the percentage predicted distance covered (based on percentage of the age and gender-specific normative values for Indians) will also be reported (Agarwal et al., 2016). Second, we do not have an objective measure of physical activity. It is not feasible in this setting to use in-built phone accelerometer apps as family members often share phones and late in monthly terms when data usage limits are reached phones are often turned off. Third, we have many secondary outcomes, and may not be powered for each. This also raises potential for inflated error due to multiple comparisons. Finally, some secondary outcomes are assessed via single items in the interests of minimizing participant burden. Therefore, there could be more measurement error for these.

5. Discussion

If results of this novel trial of women-focused eCR in an LMIC demonstrate clinically-significant increases in functional capacity, this could represent an important development for the field considering not only would this be an important outcome for women, but this also translates to lower mortality (Myers et al., 2002). Moreover, the intervention has been designed to be affordable from a health system perspective, feasible to implement from a CR program perspective, and patient-centered and thus readily-adoptable by women. Thus, after making appropriate improvements based on findings, it could be readily scaled-up for a future multi-centre trial powered for mortality and/or morbidity outcomes and with an ancillary health economic analysis. With regard to implementation, TaCT could be sustainable in the local CR program and beyond (Subedi et al., 2020). The intervention may also be appropriate for translation to other South Asian languages, where the same cultural mores around diet for example are relevant. This trial may bolster

accumulating evidence supporting the impact of CR and feasible implementation of eCR in LMICs (Mamataz et al., 2022), but extend it to a model to meet the needs of under-represented women, who are in great need.

5.1 Progress to date

To date, we have developed the CR program content included in the "Sukhi Hrudaya" website and the android mobile application. A video on Pranayama and meditation was prepared. The bi-weekly call template, text messages and information to send through the WhatsApp was also prepared. The materials have been translated and finalized. The pilot study started in March 2022. We will be starting data collection for the full trial in October 2022, giving the technology-based comprehensive CR intervention for 6 months. We expect to complete the 6-month post-test assessments in the accrued cohort by July 2023.

List of abbreviations

CR: Cardiac Rehabilitation;

CVD: Cardiovascular Disease; DASI: Duke Activity Status Index;

GAD-7: Generalized Anxiety Disorder;

GPAQ: Global Physical Activity Questionnaire;

ICRR: International Cardiac Rehab Registry;

LMICs: Low and Middle-Income Countries;

eCR: Electronic Cardiac Rehabilitation;

QoL: Quality of Life;

RCT: Randomized Controlled Trial;

SMS: Short Message Services;

TaCT: Technology-based Comprehensive Cardiac Rehabilitation Therapy;

WHO: World Health Organization;

Ethics approval and consent to participate

The trial protocol has been reviewed and approved by Kasturba Medical College and Kasturba Hospital Institutional Ethics Committee in December 2020 (IEC: 471/2020). In accordance with the Declaration of Helsinki, informed consent will be obtained from all participants before being enrolled in the study. The identity of the participants, as well as the confidentiality of the data collected will be strictly maintained throughout the study and made accessible to only the core investigation team. All publicly-available data will be anonymized and accessible only upon written request to the Principal Investigator.

Consent for publication

This manuscript does not contain the data of individual persons in any manner; hence this is not applicable.

Availability of data and materials

Not applicable

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Fig 2. Piloted TaCT CR Intervention

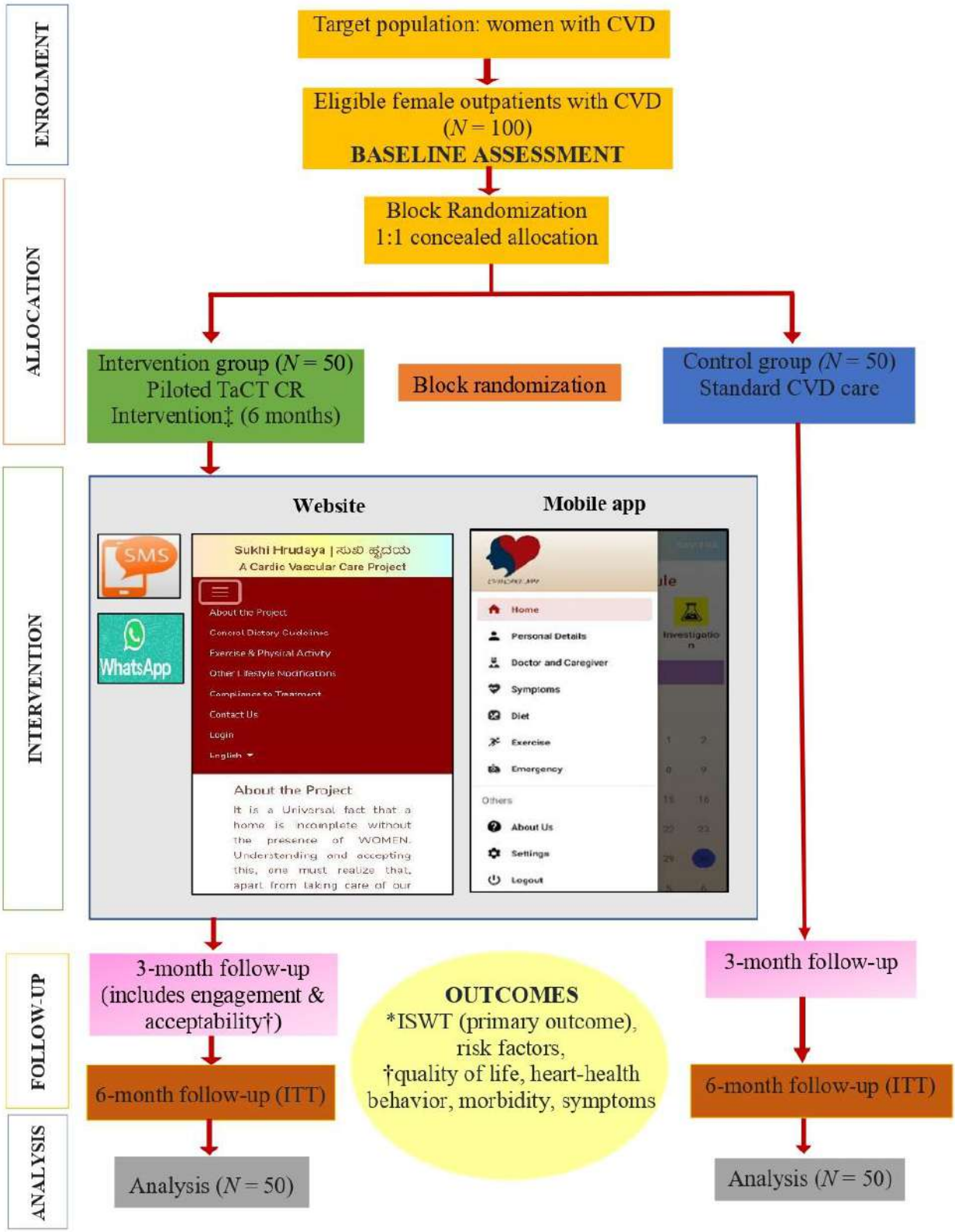

Figure 1. CONSORT flow diagram for the TaCT trial

*assessed at baseline and 6 months only; †assessed at baseline, 3 months and 6 months; ‡also includes standard care

Key: CVD: Cardiovascular Disease; ITT: Intention-to-treat; CR: Cardiac Rehabilitation; TaCT: Technology-based Comprehensive Cardiac Rehabilitation Therapy; ISWT: Incremental Shuttle Walk Test, SMS: Short Text Message

Supplementary file 1. TaCT Trial Bi-weekly call template

Participant ID # _____

Date: _____

Call # _____ (of 12 calls)

Before the call: Review preferred language of participant, notes from last call. Review medications (and if they have coverage). Review blood pressure (BP) and lipids. Review diet and exercise prescription. Are they a tobacco user? If waist circumference above guideline, will want to check on weight. Review their goals from last time and education area.

1. Connect / rapport. How is the patient doing?
2. Any symptoms or concerns about their heart health since you last talked?
    a. Any falls, changes in medications, healthcare visits / Emergency department
3. Health behaviors:
    a. Medication adherence (if they have coverage) –
        i. Ask them which pills they are taking and when (to confirm they are following what is prescribed).
            1. If deviating, discuss with them
        ii. Did they forget to take them at any time?
        iii. Having any side effects?
        iv. When do they next need to be refilled?
    b. Exercise
        i. Ask them to report average exercise each day (frequency, intensity, time, type, and record in notes below)
            1. any symptoms during exercise?
            2. Any issues with exercising in their target range of perceived exertion?
            3. If doing well: progress? Work up to 150 mins/week
            4. If not adhering: explore barriers and have patient suggest ways to overcome them
    c. Diet
        i. Recommendations based on dietcal
        ii. Ask about processed food, salt, portion sizes
        iii. Ask about fruit & vegetable intake
    d. Tobacco use (as applicable)
4. What areas they have read about / education – discuss / questions
    a. Based on assigned information to read on the website or app for discussion each call
5. How is their stress level?
    a. Ask about regular meditation and yoga

    b. Any psychosocial concerns? Getting sufficient support?
6. Clinical issues
    a. If they need follow-up for BP or lipids (as applicable)
        i. Does it need to be assessed again, do medications need to be titrated?
    b. Any other cardiac issues (stress or other tests upcoming, etc.)
7. Have them repeat to you their next steps based on the call overall / summarize
8. Agree on / review date and time for next call (put it in their app calendar)
    a. Suggest a page to read on the website or app for discussion next call (or ask them what they need / want to learn about; e.g., women and heart health)

NOTES:

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