STUDY PROTOCOL

Team based collaborative care model, facilitated by mHealth enabled and trained nurses, for management of heart failure with reduced ejection fraction in India (TIME-HF): design and rationale of a parallel group, open label, multi-centric cluster randomised controlled trial [version 2; peer review: 1 approved, 1 approved with reservations]

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Abstract

**Background:** Heart failure (HF) is a debilitating condition associated with enormous public health burden. Management of HF is complex as it requires care-coordination with different cadres of health care providers. We propose to develop a team based collaborative care model (CCM), facilitated by trained nurses, for management of HF with the support of mHealth and evaluate its acceptability and effectiveness in Indian setting.

**Methods:** The proposed study will use mixed-methods research. Formative qualitative research will identify barriers and facilitators for implementing CCM for the management of HF. Subsequently, a cluster randomised controlled trial (RCT) involving 22 centres (tertiary-care hospitals) and more than 1500 HF patients will be conducted to assess the efficacy of the CCM in improving the overall survival as well as days alive and out of hospital (DAOH) at two-years (CTRI/2021/11/037797). The DAOH will be calculated by subtracting days in hospital and days from death until end of study follow-up from the total follow-up time. Poisson regression with a robust variance estimate and an offset term to account for clustering will be employed in the analyses of DAOH. A rate ratio and its 95% confidence interval (CI) will be estimated. The scalability of the proposed intervention model will be assessed through economic analyses (cost-effectiveness) and the acceptability of the intervention at both the provider and patient level will be understood through both qualitative and quantitative process evaluation methods.

**Potential Impact:** The TIME-HF trial will provide evidence on whether a CCM with mHealth support is effective in improving the clinical outcomes of HF with reduced ejection fraction in India. The findings may change the practice of management of HF in low and middle-income countries.

**Keywords**
Heart failure, collaborative care model, mhealth application, cluster randomised controlled trial

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Amendments from Version 1

We have clearly stated that the intervention proposed in this trial is specific to heart failure patients with reduced ejection fraction. Details on the mHealth application and its capabilities are described in detail. The qualitative data collection during the follow-up and domains of qualitative process indicators are described in detail in the revised manuscript. The data analysis plan of the qualitative component are described in detail. The development of working analytical framework and thematic analysis are explained. Application of normalisation process theory and components of RE-AIM in the qualitative process evaluation are illustrated briefly. We have also corrected inadvertent errors in the Table 3 with regard to measurement of parameters at baseline and during follow-up.

Any further responses from the reviewers can be found at the end of the article.

Introduction

Globally, heart failure (HF) is a major public health problem with relatively high morbidity and mortality. The number of individuals with HF is estimated to be in the range of 1.3 to 4.6 million in India[1-3]. Additionally, the number of deaths due to HF in India showed an increase of 138 percent from 1990–2013[4]. Based on the best available estimates, the incidence of HF in India is 1 per 1000 population[5]. In consistent with findings from many high-income countries, the predominant etiology of HF is ischemic heart disease (IHD) in India[6]. Due to the steady increase in the absolute number of individuals with IHD over the last three decades[6,7], HF burden is expected to grow substantially in India.

Heart failure patients in India receive sub-optimal treatment and experience high mortality. For example, only one of four eligible HF patients receives guideline-directed medical therapy (GDMT) at discharge[6,8]. Similarly, one of three patients adhered to GDMT in a large study in India involving 15,870 patients with reduced left ventricular ejection fraction (EF<40%)[9]. Additionally, one of five patients died within three months of follow-up[9]. The long-term prognosis of HF is also poor with a median survival time of 3.7 years[10]. However, those who received GDMT experienced lower mortality and survived longer[10]. Data from the Kerala Heart Failure Registry[11], and the National Heart Failure Registry[12] also demonstrated survival benefits in patients who received GDMT during index hospitalisation. Further, the survival benefits of GDMT persisted up to five years of follow-up[10].

Physician driven quality improvement initiatives in HF management may not be feasible, scalable, and effective in India. The PINNACLE India quality improvement programme concluded that in a country with a disproportionate provider/patient ratio and low levels of government funding for quality improvement, physician-driven initiatives for practice-based learning and improvement are extremely difficult[13]. The key barriers include lack of electronic medical records, virtually non-existent outpatient record-keeping, and difficulty of engaging physicians due to their busy clinical schedules[14]. To overcome these barriers, we propose a task sharing strategy of empowering trained nurses as facilitators of HF care in India.

A specially trained nurse facilitating the management is a viable alternative strategy in the management of HF[12-16]. In general, specialist HF nurses share the role of a physician, assess the patients, and manage them based on the tested protocols/algorithms. Additional roles for nurses include psycho-social aspects of self-management of the condition in home settings[16], communicating self-care guidelines[17], and regular monitoring of patient conditions even when they are away from the hospital or outpatient settings. These strategies in general are effective in achieving improved physical functioning, reduced hospital length of stay and increased adherence towards pharmacological therapy in high-income settings. Three recent meta-analyses also show that task sharing strategy, especially involving nurses in management of cardiovascular risk conditions such as hypertension[18], dyslipidemia[19] and diabetes[20] is effective in achieving desirable outcomes even in low and middle-income countries (LMIC).

The collaborative care model (CCM) based on Wagner’s Chronic Care Model[21] is proposed as a key strategy in the management of HF. For example, CCM results in improvements in hospitalisation rates[22,23] and quality of life[24], and reduction in cost associated with management of HF[24-27]. Additionally, increased use of GDMT and improved self-care are also attributed to interventions based on CCM[28]. However, most of them are small single centre studies leading to reduced validity and reliability of their findings. We propose to develop a CCM, facilitated by trained nurses, for management of HF with reduced ejection fraction (HFrEF) and evaluate its acceptability and effectiveness in Indian settings.

The major aims of the study are as follows: (1) to identify barriers and facilitators for implementing a team based CCM for the management of HF, (2) to assess the efficacy of the CCM in improving the days alive and out of hospital (DAOH) at two-year follow up in patients with HFrEF and (3) to evaluate the scalability of proposed intervention model; (a) to evaluate the overall cost-effectiveness of the intervention strategy, (b) at the provider level, to assess the ease of using the protocols/mHealth application, impact on work load, and satisfaction, and (c) at the patient level, to explore risk-perception, ease of seeking health care, utility of understanding risk and addressing warning signs/symptoms on a real time basis, changes made to health behaviours and adherence to guideline directed therapies.

Methods

Ethical considerations

The participants will be informed about the study and provided with a detailed information sheet[29]. Trained research nurse appointed by the principal investigator will obtain written informed consent from all study participants. The research
study is approved by institutional ethics committee of Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTIMST) and of the participating centres (SCT/IEC/1691/ AUGUST-2021). The study protocol is registered with the clinicaltrials.gov (CTRI/2021/11/037797). All changes in the trial protocol will be informed to the institutional review boards.

All serious adverse events will be reported immediately to the respective ethics committees of the participating centres and the study co-ordinating centre (SCTIMST). The principal investigators (PIs) will have access to the final data set. Public access to the data set after de-identification will be provided upon formal request with necessary permission from the SCTIMST ethics committee after three years from the date of completion of the study.

Study design approach
The proposed study will use mixed methods to achieve the study aims. The design approaches will include: Aim 1- formative qualitative research, Aim 2- a multi-centric cluster randomised controlled trial (RCT), and Aim 3- cost effectiveness and evaluative qualitative research. We will follow the Medical Research Council (UK) guidance on developing and evaluating complex interventions\(^1\) and guidance for reporting intervention development studies in health research\(^2\). The trial duration will be from September 2021 to August 2026\(^3\).

The protocol design is based on the Standard Protocol Items: Recommendations for Intervention Trials (SPIRIT) Checklist\(^4\). The SPIRIT flow chart shows the schedule of enrolment, interventions, and assessments of TIME-HF trial\(^5\).

**Formative qualitative research (Aim 1)**
In-depth interviews with multiple stakeholders like patients, carers, nurses, community health workers, primary care physicians, and cardiologists will be conducted (Table 1). Interviews with nurses and cardiologists will be face-to-face, semi-structured and include questions regarding HF care integration. Additional in-depth interviews will be conducted with dieticians, specialist physiotherapist and clinical psychologists to get their perceptions of CCM. In-depth interviews with adult HF patients will gather information on their understanding of diseases, barriers and facilitators to care, and feedback on the proposed intervention components (lifestyle education, disease management program, pharmacologic treatment, self-care, and care coordination). Similarly, in-depth interviews of adult carers of patients with HF will gather information on self-management and care coordination. The number of interviews will be determined based on thematic saturation in each category. The stakeholders for the interview will be selected from hospitals with facilities for management of HF. The intervention and trial protocols will be modified by incorporating key findings from the qualitative study.

**Collaborative care model intervention (Aim 2)**
A parallel group cluster RCT of more than 1500 adult HF patients with reduced ejection fraction from 22 units in India\(^6\) will be used to address Aim 2. Each participating unit will be randomly assigned to one of two arms: 1) those delivering a comprehensive CCM (intervention) or 2) those delivering standard care (usual care).

The selected hospitals will be independent units with dedicated staff employed at each site for recruitment and follow-up of patients included in the trial. The site teams will have similar compositions in terms of clinical roles.

Cluster eligibility criteria: Eligible units will include HF centres of major hospitals from the national heart failure registry or Kerala heart failure registry that serve ≥80 new patients in six-months and consented to the randomisation plan. All HF patients will also be required to provide individual consent to participate in the study.

Patient eligibility criteria and randomisation: Potential participants must meet the standard definition of HF\(^7\) (HF with reduced ejection fraction of <40%) based on echocardiography to be eligible to enter the study. Consecutive patients will be recruited from the participating centres. Eligible units will be randomised at one time point, prior to trial implementation. The allocation ratio will be 1:1. Randomisation procedures will not be blocked, restricted, or matched. We will use computer generated random numbers to allocate half of the units to each arm of the study.

**Duration of treatment period and follow-up**
We will conduct a rolling recruitment over a period of six-twelve months. Each patient in the study will be followed-up for a period of two years from the date of recruitment. The first follow-up visit in the intervention arm will be conducted on the seventh day. Additional two follow-up visits for clinical status occurs at an interval of three-months. Participants are subsequently seen no less than every six months. Regardless of the treatment group assigned, we will follow-up all study participants in this manner (assessment at 7-th day will be only in the intervention arm) until study completion.

**Measurements in the study**
A structured questionnaire\(^8,9\) will be administered by trained research nurse to collect relevant data at baseline, and every three months until two years from baseline. At these visits, interval assessments of HF and angina symptom status, current use of medications, and clinical endpoint data including hospitalisations and procedures since the previous visit will be documented (Table 2). The baseline questionnaire includes assessments of demographic and socioeconomic variables, general health status, aetiology, history and risk factors, diet pattern, physical activity, tobacco, and alcohol consumption, quality of life, and six minutes walking distance. Depression and anxiety scores will be collected from each participant by using Patient Health Questionnaire-9 (PHQ-9)\(^9\) and Generalized Anxiety Disorder Questionnaire (GAD-7) at baseline and during follow-up visits\(^10\). Medication adherence will be measured using four item Morisky Green Levine medication adherence scale during the follow-up visits\(^11\). The follow-up study questionnaire will also
### Table 1. Formative qualitative methods.

<table>
<thead>
<tr>
<th>Participants</th>
<th>Methods/Number</th>
<th>Topics</th>
</tr>
</thead>
</table>
| Patients with HF both male and female in various age groups | In-depth interview Total 10–12 IDIs           | ● Perceptions and behaviours on clinical management, lifestyle, and self-care  
● Feedback on proposed intervention components and methods  
● Assess patients' interest and acceptability |
| Caregivers of patients with HF | In-depth interview Total 10–12 IDIs           | ● Perceptions and behaviours on clinical management, lifestyle, and self-care  
● Feedback on proposed intervention components and methods  
● Gauge caregivers' interest and acceptability |
| Physicians, Nurses, Dieticians, Physiotherapists | In-depth interview 10–12 interviews in each category (30–36 total interviews) | ● Perceived quality of HF care  
● Perceived patient barriers and facilitators to delivery of care, lifestyle change, and self-care  
● Gauge feasibility of planned intervention components |

### Table 2. Study measurements in TIME-HF.

<table>
<thead>
<tr>
<th>Study measurements</th>
<th>Method/Instrument</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure in mmHg</td>
<td>Electronic BP monitor</td>
</tr>
<tr>
<td>Height in cm</td>
<td>Stadiometer</td>
</tr>
<tr>
<td>Weight in kg</td>
<td>Digital weighing scale</td>
</tr>
<tr>
<td>Waist circumference in inches</td>
<td>Non elastic measuring tapes</td>
</tr>
<tr>
<td>Etiology and risk factors</td>
<td>Details of the etiology and risk factors using a questionnaire</td>
</tr>
<tr>
<td>Investigations</td>
<td>Blood reports, ECHO, ECG reports</td>
</tr>
<tr>
<td>Current Medication</td>
<td>Details of all medications the patient was taking at the time of contact</td>
</tr>
<tr>
<td>Depression</td>
<td>PHQ-9[^40^]</td>
</tr>
<tr>
<td>Anxiety</td>
<td>GAD-7[^41^]</td>
</tr>
<tr>
<td>Self-management</td>
<td>Morisky, Green and Levine medication adherence scale[^42^], weight management[^36^], Diet Management[^25^], Family support[^24^], Patient care in depression[^23^]</td>
</tr>
<tr>
<td>Quality of life</td>
<td>KCCQ[^43^], EQ-5D-5L[^44^],[^45^]</td>
</tr>
<tr>
<td>Walking ability</td>
<td>6 Minute Walk Test[^46^]</td>
</tr>
<tr>
<td>Physical disability (muscular strength)</td>
<td>Hand grip strength- Dynamometer</td>
</tr>
<tr>
<td>Frailty</td>
<td>Fried frailty index[^47^],[^48^]</td>
</tr>
<tr>
<td>Functional capacity</td>
<td>Specific Activity Questionnaire[^48^]</td>
</tr>
<tr>
<td>Physical activity intensity</td>
<td>The Borg Scale of Perceived Exertion[^49^]</td>
</tr>
<tr>
<td>Disease severity</td>
<td>Modified Borg Dyspnea Scale during 6MWT (0 – 10)[^50^],[^51^], Responsiveness to change in heart failure symptoms[^38^]</td>
</tr>
<tr>
<td>Treatment burden</td>
<td>MTBQ[^52^]</td>
</tr>
<tr>
<td>Patient satisfaction</td>
<td>Patient satisfaction in Quality of care[^50^], Care transitions measure (CTM3)[^53^],[^54^]</td>
</tr>
</tbody>
</table>

[^40^]: PHQ-9- Patient Health Questionnaire- 9,  
[^41^]: GAD-7- Generalised Anxiety Disorder Questionnaire,  
[^42^]: KCCQ- Kansas City Cardiomyopathy Questionnaire,  
[^43^]: EQ-5D-5L- EuroQol 5dimension -5 level,  
[^44^]: 6MWT- Six Minute Walk Test,  
[^45^]: MTBQ- Multi-morbidity Treatment Burden Questionnaire,  
[^46^]: ECHO- Echocardiogram,  
[^47^]: ECG- Electrocardiogram.
assess the patient satisfaction in quality of care, and family support.

Kansas City Cardiomyopathy Questionnaire (KCCQ)\textsuperscript{30} and EQ-5D-5L\textsuperscript{31} will be used to measure quality of life.

A standard adjustable handgrip dynamometer will be used to measure handgrip strength. Three measurements will be taken in dominant and non-dominant hand. The average of the highest value of dominant and non-dominant handgrip strength will be used in the analysis.

The six-minute walk test (6MWT) will be measured during the baseline and follow-up visits by following the standard protocol\textsuperscript{32}. Before the 6MWT, the research nurse will measure blood pressure, pulse, and oxygen saturation with the help of a pulse oximeter. During the test, participants will have to walk for six minutes. After the test, staff will record the distance covered along with oxygen level, pulse rate and post walk Borg dyspnoea levels.

Treatment burden will be assessed by using multimorbidity treatment burden questionnaire (MTBQ)\textsuperscript{33}. Health care expenditure data will be collected every six months using a treatment expenditure questionnaire\textsuperscript{34}. Clinic based blood pressure will be obtained during clinic visits. Blood will be collected at six-month interval to assess renal function and serum electrolytes. Further, we will collect data on beta-natriuretic peptides at baseline, and follow-up visits, if they are routinely done as part of the patient care. The detailed study measurements at baseline and during the study period are explained in Table 3.

Study intervention overview
All patients receiving care at a unit randomised to the usual care arm will receive the same standard of care, while all patients receiving care at units randomised to the intervention arm will receive the CCM based care.

Usual care arm: The treating physician will provide care for patients at the units that are randomised to the usual care arm. However, the physician will be assisted by a clinical coordinator to capture relevant demographic, clinical and biochemical variables of interest, and data regarding cost of care, patient satisfaction, and quality of life by using a structured interview schedule.

Intervention arm: The intervention will leverage the existing management practices at each site to deliver a comprehensive, integrated HF care led by a trained nurse with support from physicians, dieticians, physiotherapist, and clinical psychologists (Figure 1). Information from the formative research will be scientifically integrated into the comprehensive management programme. The nurses will be enabled with mHealth technology to facilitate care delivery.

Two linked mHealth applications (patient and nurse applications) will be developed exclusively for the trial. The nurses, doctors and patients involved in the study will get customised access to the mHealth application. The mHealth application will allow for real time communication between the patients and the concerned nurses in the study. Nurses will be able to communicate also with the treating physician through the application. The mHealth patient application will be made available in Google Play. During the recruitment, the patient application will be installed in the patient’s phone. The concerned nurse will be able to generate a secure secret code with the help of their mHealth application, which will be essential to formally onboard the patient in the mHealth application.

The patient application will be enabled with options to update risk factors, anxiety levels, depression, and warning signs and symptoms of HF. Further, there will be options to send images, text, and voice messages. Every week the mHealth application will push a weekly survey instrument to the patient, which will cover interval assessments of HF, activities of daily living, and symptoms and warning signs. Based on the severity of the signs and symptoms reported, the application will generate amber and red alerts to the nurses. The nurses will be required to respond to those alerts immediately using their mHealth application based on the severity of the alerts and the reaction time to respond to those alerts will be documented. There will be options to modify the prescription of the patient through the mHealth application. Although the nurses can initiate the prescription change and recommend modifications, it will require approval from the treating physician. Once approved by the treating physician, the new prescription will automatically get updated in the patient application. The patients will be able to download the modified prescription using their mHealth application.

The intervention will consists of three phases (Figure 2); 1) screening and risk stratification, 2) lifestyle modification support (nutritional education, tobacco and alcohol cessation, exercise or activity planning, daily weight monitoring, assessment of the need for cognitive behavioural therapy, and identification of warning clinical signs) and pharmacologic management, and 3) nurse facilitated and mHealth assisted disease management program, self-care management program, active follow-up and continuous monitoring of clinical conditions of the patient while the patient is away from the hospital settings.

Evaluate the scalability of proposed intervention model (Aim 3)
Cost effectiveness and acceptability analyses
Information for economic analyses will be collected during the trial to obtain detailed resource consumption. A top-down approach will capture implementation costs from a health systems perspective by quantifying the resources deployed. Some of these will be once only activities (e.g., development of a mobile telephone application) but most will be recurring (e.g., nurse hours per year). We will then cost these resources according to unit costs in India. A bottom-up approach will collect patient level out of pocket expenditure and other personal financial losses or gains. It will include human resource costs, doctor visits, laboratory tests, cost of...
medications, and co-payments for medications. Rates of outpatient (specialty clinic) visits, hospitalisations, and clinical events will also be obtained. Indirect costs (travel, missed work time, and lost productivity) incurred by patients will be estimated using questionnaires that have been used in other South Asian studies\textsuperscript{54}.

We will collect qualitative data during the follow-up period. In depth interviews with patients, nurses and clinicians will be conducted to understand the adoption and acceptability of the intervention (Table 4). Qualitative data collection approaches will be employed for prospective process measure evaluation during the trial. Process measures will include quality of care (patient centredness, safety, equity, access, and timeliness), and individual, organisational and system factors influencing effective roll-out of the intervention (causal mechanisms and contextual factors, further barriers and facilitators and motivators). The acceptability of the trial intervention among providers and patients, the feasibility of integrating and sustaining the program in the existing health care system

<table>
<thead>
<tr>
<th>Study Measurements</th>
<th>B</th>
<th>F 3M</th>
<th>F 6M</th>
<th>F 9M</th>
<th>F 12M</th>
<th>F 15M</th>
<th>F 18M</th>
<th>F 21M</th>
<th>F 24M</th>
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<tr>
<td>Blood Pressure (in mmHg)</td>
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<td>Waist circumference (in inches)</td>
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</table>

PHQ-9: Patient Health Questionnaire- 9, KCCQ- Kansas City Cardiomyopathy Questionnaire, GAD-7- Generalised Anxiety Disorder Questionnaire, MTBQ- Multi-morbidity Treatment Burden Questionnaire, 6MWT- Six Minute Walk Test, CTM-3- Care Transitions Measure
will be also assessed. Additionally, by using a close-out questionnaire, we will also ask patients to self-report their compliance to individual elements of the intervention. Data from follow-up visits questionnaire will also capture key quality indicators (Table 5). The key domains of quality will include access, timeliness, safety, patient centredness, and equity. We will describe fidelity to the intervention package components, types of changes made by healthcare organisations, how the changes were implemented, and identify multi-level contextual factors and causal pathways that affect implementation, process, and outcomes. We will use triangulation to integrate close-out questionnaire, follow-up questionnaire and qualitative process outcomes data.

**Trial sample size and power**

The mean difference in DAOH was assumed to be 20 days (586 Vs 566 days with a standard deviation of 69 days) at two-year. We used the DAOH at two-year from the Trivandrum Heart Failure Registry in the sample size calculation. In the intervention group, we assumed 3% higher DAOH. A sample size of 770 HF participants per group (a total of 1540), in 11 equal clusters per arm (total 22 clusters) provides 91% power for a 2-sided 5% alpha. Assumptions; an ICC of 0.01 (design effect 2.08), coefficient of variation of cluster size of 0.85.

**Study coordination**

Sree Chitra Tirunal Institute of Medical Sciences and Technology (SCTIMST), Trivandrum, India will be the study coordinating centre and trial sponsor. There will be 22 participating centres in India including SCTIMST. Hospitals with facilities for management of HF will serve as the cluster units or participating centres. Each participating centre will be recruiting 70 patients.

**Data entry and data management**

Qualitative data will be collected by trained post-doctoral fellows and research fellows using in-depth interview guide for each stakeholder. All the interviews will be audio-recorded with permission of the participants.

Quantitative data will be collected by trained nurses or research co-ordinators using study questionnaire. Training will be provided for collection of clinical data and personal data from the patients. Nurses/research co-ordinators under the supervision of a principal investigator and the study post-doctoral fellows will do data entry on REDCap application using a tablet computer. The data will be cleaned, queries enquired and analysed by study post-doctoral fellows and research fellows. The study will collect both quantitative and qualitative data. The data will be de-identified to ensure confidentiality of the data.

**Data analysis plan**

Aim1: All interviews conducted in local language (Malayalam) will be simultaneously translated to English and transcribed. Interviews conducted in English language will be transcribed. The data analysis will follow a framework method of analysis. After the data is transcribed, the transcripts will be read line-by-line to get familiarised with the data. First a few transcripts will be coded using an inductive method. Later, a working analytical framework will be generated by merging the initial codes. The working analytical framework will then be used to index the remaining interviews. After indexing all the interviews, key themes will be generated by merging categories having similar meaning for each stakeholder. Finally, the data will be interpreted based on the convergences and divergences between the data themes across different stakeholders.
Aim 2: All quantitative analysis will follow guidelines of cluster randomised trials [56]. We will employ intention to treat analysis except in the sub-group analyses. Initially, baseline characteristics will be compared by treatment group to examine the adequacy of randomisation. The primary analysis will be a complete case analysis. However, missing data on outcome variables will be reported and sensitivity analyses will be conducted after multiple imputation of missing data.

The DAOH will be calculated by subtracting days in hospital and days from death until end of study follow-up from the total follow-up time of 730 days. The DAOH is a patient-centred outcome, which accounts for multiple events over the two-year course of a study period, weights death more than hospitalisation, and deaths occurring early more than those occurring later. Empirical density curves will be created to show the distribution of DAOH over two-year follow-up period, stratified by intervention group. The median and the interquartile range of DAOH by treatment group will be provided. Poisson regression with a robust variance estimate [57] and an offset term to account for clustering will be employed in the analyses of DAOH per two-years of follow-up time. This procedure will yield a rate ratio and 95% CI [57]. The rate ratio is the DAOH in the intervention arm divided by...
Table 4. Qualitative methods to understand the adoption and acceptability of interventions.

<table>
<thead>
<tr>
<th>Participants</th>
<th>Methods/Number</th>
<th>Topics</th>
</tr>
</thead>
</table>
| Patients with HF both male and female in various age groups | In-depth interview Total 10-12 IDIs | • Quality of care (safety, patient centeredness, equity, access, timeliness)  
• Satisfaction and adherence to intervention.  
• Factors contributing to use/refusal of intervention.  
• Suggestions for modification. |
| Physicians Nurses, organisation leaders and implementers | In-depth Interviews 10-12 interviews in each category (20-24 total interviews) | • Quality of care (safety, patient centeredness, equity, access, timeliness)  
• System related barriers for adoption of intervention.  
• Barriers at patient level.  
• Satisfaction and suggestions for modifications. |

Table 5. Performance indicators in TIME-HF.

<table>
<thead>
<tr>
<th>Performance indicator</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In-patient measures</strong></td>
<td></td>
</tr>
<tr>
<td>Evaluation of left ventricular systolic (LVS) function</td>
<td>Proportion of HF patients with LVS function assessed before arrival, during hospitalisation, or is planned after discharge.</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitor (ACEI), or angiotensin receptor blocker (ARB) for left ventricular systolic dysfunction (LVSD)</td>
<td>Proportion of HF patients with LVSD and without both ACEI and ARB contraindications who are prescribed ACEI or ARB at hospital discharge.</td>
</tr>
<tr>
<td>Anticoagulant at discharge for HF patients with atrial fibrillation (AF)</td>
<td>Proportion of HF patients with AF and without contraindications who are prescribed warfarin or NOACs at discharge.</td>
</tr>
<tr>
<td>Clinical handover</td>
<td>Proportion of HF patients discharged home with written instructions addressing all of the following: activity level, diet, discharge Medications, follow-up appointment, weight monitoring, and what to do if symptoms worsen.</td>
</tr>
<tr>
<td>Adult smoking cessation advice/counselling</td>
<td>HF patients with a history of smoking cigarettes, who are given smoking cessation advice or counselling during hospital stay.</td>
</tr>
<tr>
<td><strong>Outpatient measures</strong></td>
<td></td>
</tr>
<tr>
<td>LVS function assessment</td>
<td>Proportion of HF patients with documentation that LVS has been assessed.</td>
</tr>
<tr>
<td>Weight measurement</td>
<td>Proportion of patients with measurement of weight at each outpatient visit to assess change in volume status.</td>
</tr>
<tr>
<td>Blood pressure measurement</td>
<td>Measurement of patient’s blood pressure and calculation of pulse pressure at each outpatient visit.</td>
</tr>
<tr>
<td>Assessment of clinical signs and symptoms of volume overload (excess)</td>
<td>Assessment of clinical symptoms of volume overload at each outpatient visit (e.g., dyspnoea, orthopnoea). Signs include peripheral oedema, rales, hepatomegaly, and ascites. Proportion of patients without hypoperfusion and congestion.</td>
</tr>
<tr>
<td>Assessment of activity level</td>
<td>Proportion of patients with evaluation of the impact of HF on activity level at each outpatient visit.</td>
</tr>
<tr>
<td>Patient education</td>
<td>Percentage of patients who were provided with patient education on disease management and health behaviour changes during follow-up visits.</td>
</tr>
<tr>
<td>Beta-blocker therapy</td>
<td>Prescription of beta-blockers in patients with HF and LVSD. Adherence to Beta-blocker therapy at follow-up visit.</td>
</tr>
<tr>
<td>ACEI or ARB therapy for patients with HF who have LVSD</td>
<td>Proportion of patients with prescription of ACEI or ARB for management of outpatients with LVSD. Adherence to ACEI or ARB therapy at follow-up visit.</td>
</tr>
<tr>
<td>MRA for patients with HF</td>
<td>Prescription of MRA for management of outpatient with LVSD. Adherence to MRA therapy at follow-up visits.</td>
</tr>
<tr>
<td>Warfarin therapy for patients with AF</td>
<td>Proportion of HF patients with chronic/recurrent AF and without contraindications who are adherent to warfarin/NOACs at follow-up.</td>
</tr>
<tr>
<td>Assessment of depression</td>
<td>Proportion of patients with assessment for depression</td>
</tr>
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</table>

NOACs- Novel oral anticoagulants, MRA- Mineralocorticoid Receptor Antagonists
DAOH in the enhanced usual care arm. A rate ratio of >1 indicates more DAOH in the intervention arm in comparison to the usual care arm (i.e., favours the intervention).

Multilevel mixed-effects survival models will be employed for analyses of time to secondary outcomes (composite of mortality and hospitalisation). A random term identifying the location of participating sites will account for the clustering effect. We will also conduct a landmark analysis conditional upon intervention group membership at 30 days of follow-up. The between-group differences for each of the secondary outcomes (other than binary outcomes variables) will be measured using mixed-effect linear models and after accounting for clustering of observations. Standard errors will be calculated using robust estimation procedures69.

Pre-specified sub-group analyses (age group, sex, region, type of facility, clinical severity) will be conducted. The significance of subgroup effects will be assessed by tests of interactions of covariates and the treatment effect.

Finally, as an exploratory analysis we will also use win ratio69 to analyse the composite secondary outcome of mortality and hospital admissions. The win ratio statistic prioritises the mortality and hospitalisation endpoints through sequential comparisons. Patients in the intervention and usual care group will be converted into matched pairs based on their baseline risk profiles. The intervention patient will be labelled as a ‘winner’ or a ‘loser’ depending on who died first. If there is no death, the pairs will be labelled a ‘winner’ or ‘loser’ depending on who had a hospitalisation first. Otherwise, they are considered tied. Finally, the win ratio will be generated, which is the total number of winners divided by the total numbers of losers. A 95% confidence interval and P-value for the win ratio will be obtained. If matched pairs are not possible, the analyses will be conducted on unmatched pairs.

The data on costs for the intervention and control groups will be compared to assess Incremental Cost-Effectiveness Ratios (ICER), the differences in outcomes between the intervention and control groups versus differences in costs of the intervention components. ICER measures will include the cost per case of primary outcome avoided. If the primary clinical outcomes are shown to differ significantly between group, a full economic evaluation of the lifetime costs, benefits, and cost-effectiveness (in life years gained) comparing the usual care to intervention strategy will be performed. Decision models from health system and societal perspectives, a lifetime analytic horizon, and 3% discounting of future costs and outcomes will be used. QALYs will be derived from EQ5D-VAS. We will also estimate the economic rate of return of an additional rupee spent on the intervention, with the return being in the form of knock-on costs of health services saved. For this purpose, the costs of the intervention will be the direct and indirect costs for the intervention components but excluding knock-on costs on health service use. The differences in the costs of health service use in the treatment and control participants will be used to construct an estimate of monetary savings. The ratio of these (discounted using 3%) savings and intervention costs, will be used to derive the economic rate of return over 2-years from the start of the intervention.

Aim3: All interviews conducted in local language (Malayalam) will be simultaneously translated to English and then transcribed by the post-doctoral and doctoral level fellows engaged in the study. Interviews conducted in English language will be transcribed. Field notes will be collected as part of process evaluation. Qualitative analysis will be done using a thematic analysis. A deductive coding approach will be done using the Normalisation Process Theory (NPT)61, which will help to determine factors that promote or inhibit the incorporation of interventions into routine work. The findings will be interpreted using components of the RE-AIM61 (Reach, Efficacy, Adoption, Implementation and Maintenance) framework to help inform the adoption, likelihood of adoption and key predictors of integrating and continuing the new care model.

Study outcomes
Primary outcome is the days alive and out of hospital (DAOH) during the two-year follow-up period. Major secondary outcomes include; a) a composite endpoint of mortality (all-cause) or hospitalisation (>24 hours) during study follow-up period, b) six minutes walking distance, c) adherence to GDMT and d) quality of life.

Data safety and monitoring
The central team will review the data on real-time basis and feedback will be provided to the participating sites. Periodic monitoring of the data will be done once in six months. Source data verification of 10 percent of the data fields will be conducted. A data safety monitoring board (DSMB)60 with members independent of the trial will review the trial outcome and data safety annually.

Discussion
Heart failure is a chronic condition with a wide range of effects on the activities of daily living and require lifelong management. There have been considerable advancements in the treatment and management of HF in the recent past. Despite these developments, HF patients still experience high treatment burden, reduced quality of life, frequent hospitalisations, and death63. A team-based approach involving task sharing with different cadres of health care providers may be best suited for management of a multimorbid condition like HF in Indian settings.

Guideline directed medical treatment is the main pillar of chronic management of HF with reduced EF64,65. One of the challenges in HF management is the implementation of complex treatment regimens especially for those with co-morbidities and the effective tracking of patients to monitor the disease progression. A patient who has been initiated on GDMT needs careful monitoring and close follow-up for titration of the medication. Although the benefits of GDMT in the management of HF have been documented, there exists a gap in the provisioning and the adherence of GDMT66.
At the patient level, the requirement of frequent travel to the clinic to manage their conditions is a barrier and an important limiting factor in ensuring continuity of care. Strategies to improve adherence to GDMT should therefore explore patient related barriers and address them effectively.

Timely monitoring of the symptoms of congestion and the effective implementation of healthy behaviours into the daily lives are additional challenges in HF management. Given the effectiveness of the task sharing strategy of enabling nurses in management of cardiovascular conditions, monitoring patients remotely with a specially trained nurse, and nurses acting as care coordinator in a team-based care model with support from physicians and other health care providers are viable strategies to improve HF outcomes in low resource settings.

The mHealth application facilitates real-time monitoring of the warning signs and symptoms of worsening HF. The patients will be advised to update risk factors, anxiety levels, depression, warning signs and symptoms of HF through the mHealth application. In addition to the daily monitoring of the patients, they are also advised to report a weekly survey. This can help the nurses and the doctor to make informed and timely decisions on management of the patients and prevent the need for hospitalisation due to exacerbations or worsening of the condition.

Although CCM has been a successful model in high-income settings for management of chronic conditions, there is still a lack of understanding on the acceptability, and feasibility of this model among patients and providers in India and other LMICs. Our trial will explore the acceptability and feasibility of CCM the Indian settings. We will also investigate the overall cost-effectiveness of the intervention strategy. The effect of CCM on mental health conditions like depression and anxiety is promising. Since HF is a multimorbid condition and often co-exists with mental health conditions, CCM may have important role in improving the quality of life, and physical functions of the patients compared to routine care. In our trial, the CCM will be developed based on the inputs from various stakeholders like doctors, nurses, patients, and their caregivers. This will help us to design a contextually relevant and patient-centred approach in management of HF.

Implications

The findings of TIME-HF trial will have the potential for changing the care delivery of HF and other chronic conditions in India. The knowledge generated from TIME-HF study will identify the system-level changes needed to address the limitation of the current care for HF. The collaborative care model has the potential to improve the communication and collaboration between specialists, nurses, and other stakeholders for a comprehensive care delivery for HF. The remote monitoring, early identification of the warning signs and symptoms of worsening of disease conditions, and timely management may help to prevent hospitalisation and mortality in HF patients.

Dissemination

The key-findings will be published in leading academic journals as well as it will be presented in conferences. Policy implication of the study findings will be developed, and it will be shared with various stakeholders at the state, regional and national level.

Study status

At the time of protocol submission, all participating sites had been identified and recruitment of patients started. The data collection is planned to be completed by 2025.

Data availability

Underlying data

No data are associated with this article.

Extended data

Figshare: Structured Questionnaire
https://doi.org/10.6084/m9.figshare.21802917.v1

The file “Structured Questionnaire” contains the following extended data:

- Baseline Proforma
- 3rd, 6th, 9th, 12th, 15th, 18th, 21st, 24th month follow-up questionnaire

Figshare: 7th day Follow-up Questionnaire
https://doi.org/10.6084/m9.figshare.21802815.v2

The file “7th day Follow-up Questionnaire” contains the following extended data

- 7th day follow-up questionnaire for intervention arm only

Figshare: Informed Consent (TIME-HF study)
https://doi.org/10.6084/m9.figshare.22360375.v1

The file “Informed Consent (TIME-HF study)” contains the following extended data

- Participant information sheet and
- Consent form

Figshare: List of participating centres
https://doi.org/10.6084/m9.figshare.22360585

Figshare: Data Safety Monitoring Board
https://doi.org/10.6084/m9.figshare.22360561

Figshare: Timeline of TIME-HF trial
https://doi.org/10.6084/m9.figshare.22360615

Data are available under the terms of the Creative Commons Attribution 4.0 International license (CC-BY 4.0).


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Devraj Jindal

1 Centre for Chronic Disease Control (CCDC), New Delhi, Delhi, India
2 Centre for Chronic Disease Control (CCDC), New Delhi, Delhi, India

This study, conducted by Jeemon P et al between September 2021 to August 2026 focuses on the implementation of a team-based Collaborative Care Model (CCM) which would be guided by a trained nurse, for the management of Heart Failure, focusing on Days Alive and Out of the Hospital (DAOH), with the support of mHealth and to evaluate their acceptability and effectiveness in Indian setting.

The study plans to use a formative qualitative research for the purpose of identifying barriers and facilitators for implementing a team-based CCM for heart failure management; a multi centric randomised controlled trial to assess the effectiveness of the CCM in improving DAOH, cost effectiveness and evaluative qualitative research to understand the scalability of the intervention model in terms of cost-effectiveness, provider satisfaction, and patient outcomes.

The initial step is to conduct in-depth interviews with multiple stakeholders involved in the Heart Failure Management, the key findings of which would be helpful in making the intervention contextually relevant. For the CCM intervention, the study will conduct a parallel group cluster Randomised Controlled Trial with more than 1500 Heart Failure Participants from 22 units in India, each unit being randomly assigned as intervention group (CCM) and control group (standard care). There will be a rolling recruitment for 6-9 months and a structured questionnaire will be collected by the trained research nurses, at baseline and every 2 months for a period of 2 years. The CCM will be delivered in 3 phases-risk stratification, lifestyle modifications and disease management with the aid of mHealth technology (remote monitoring and decision prompts). The mHealth application facilitates real time monitoring of the warning signs and symptoms of worsening Heart Failure.

Economic analysis will be conducted during the trial, every 6 months, with a top down approach for Health Systems perspective and bottom up approach for patient-level costs. At the end of treatment, the study will assess the perspectives of patients and nurses on the quality of care,
intervention barriers, and participation benefits or disadvantages.

The primary outcome of the study over the two-year follow-up period will be DAOH, while the major secondary outcomes include a composite endpoint of mortality or hospitalization (>24 hours), 6-minute walking distance, adherence to Guideline Directed Medical Therapy (GDMT), and quality of life.

In summary, this trial aims to develop a Comprehensive Care Model (CCM) for Heart Failure management in India by incorporating input from various stakeholders, such as doctors, nurses, patients, and caregivers. The goal is to establish a patient-centred approach that prioritizes the individual needs and preferences of Heart Failure patients. The study findings have the potential to impact the delivery of healthcare for Heart Failure in India.

The authors have provided important and detailed information in the body of the manuscript. The objective, study design, and methods are clearly described. However, it would be good to know more about the intervention. I have a few queries related to the intervention:

- What are the qualifications of the nurses involved? Will these nurses be specifically hired for the project, or will existing resources be utilized for intervention delivery?
- More details about the mHealth component would be useful. Is the mHealth component compliant with the Ayushman Bharat Digital Mission (ABDM)?

Overall, the research is going to be useful for providing insights and solutions for quality care delivery for heart failure in India.

Is the rationale for, and objectives of, the study clearly described?
Yes

Is the study design appropriate for the research question?
Yes

Are sufficient details of the methods provided to allow replication by others?
Yes

Are the datasets clearly presented in a useable and accessible format?
Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: I am a public health specialist with more than ten years of experience utilizing technology and applied research at both the health system and community levels. My extensive background includes progressively designing, implementing, and leading user-centered digital health interventions that aim to enhance health outcomes.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.
Thank you very much for the positive feedback on the study protocol and the trial design. As suggested, we have added more details on the mHealth application in the manuscript text along with study intervention overview section. The patient's mHealth application is made available in the Google Play Store. We are not sure whether the mHealth component is currently compliant with the Ayushman Bharat Digital Mission (ABDM). Our technical team will evaluate the requirements and they will ensure that it is compliant with ABDM in the next revision. Thank you for this valuable suggestion.

Competing Interests: Nothing to declare.

Heather Ross
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Thank you for the opportunity to provide peer review of the study protocol prepared by Jeemon and colleagues to describe the evaluation of a team based collaborative care model for management of heart failure in India. The proposed research study seeks to employ a cluster RCT design to evaluate the effectiveness of implementing a nurse-led team-based collaborative care model for managing heart failure patients at clinics in India. This review will comment on both strengths and opportunities to strengthen the work with particular attention to the rationale, study design, and methods described in the study protocol. Several typographical errors including omitted words and errors in subject-verb agreement were noted throughout the manuscript. This review will not enumerate those, as the authors can identify and fix the issues that were likely simply an oversight.

Rationale for the Study

The authors rightly identify physician workforce challenges to address the complex work of managing patients with heart failure in the outpatient setting, along with strong evidence supporting the efficacy of nurse-led interventions to prevent re-hospitalization compared to usual care. The attention to evidence related to low and middle-income countries, and evidence from India specifically, is noted and appreciated. I note that the literature review mentions three meta-analyses, but only two are cited.
The identification of the collaborative care model (CCM) based on Wagner's Chronic Care Model is an appropriate theoretical model to guide the work. I note that the authors' phrasing suggests that the team-ness of their CCM approach is novel. However, team approaches are inherent to CCMs, and indeed Wagner's Chronic Care Model specifies a team as the healthcare delivery mechanism. With that in mind, the authors may wish to revisit the introduction section to expand the literature review to include evidence pertaining to team-based care in addition to the literature review on nurse-led care.

In addition to the Chronic Care Model as a theoretical model, I note that the proposed study seeks to implement an intervention with established effectiveness evidence, that is, the nurse-led team-based heart failure outpatient management approach. As such, the authors may wish to consider an implementation science approach (PRISM/RE-AIM) as the most appropriate framework to guide the study design.

The paragraph describing study aims would benefit from some reorganization. The sentences expanding on DAOH following aim 2 are out of place in a list of aims and may be better situated in the methods section discussion of measures. In addition, the sub-letters for aim three are not clearly related to the stated overarching aim focused on scalability. As such, the research team may wish to reconsider the notion of scalability as the overarching aim. Here, the recognition of an implementation science framework would be appropriate as it explicitly attends to issues of reach, effectiveness, adoption, implementation, and maintenance of the intervention in the target setting.

**Study Design**

The mixed-methods approach using qualitative interview including multiple stakeholder groups (Aim 1) to inform the design of a cluster RCT (Aim 2) is appropriate. The cost-effectiveness and evaluative qualitative research (Aim 3) following the RCT may be appropriate. However, the evaluation methods for Aim 3 may benefit from additional clarity as will be discussed in the following section.

The use of the SPIRIT checklist is appropriate. However, there is no clear implementation study framework noted. Again, the PRISM/RE-AIM approach would offer rigor. In addition, the protocol mentions a SPIRIT flowchart that appears to be Table 3, though it is not cited in the text in the Methods-Study Design Approach section where it is first mentioned.

Considering the RCT (Aim 2), the study design would benefit from a description of the 22 units that will compose the RCT sites. Are these units in distinct locations or catchment areas where patients are unlikely to overlap between sites? Do the units employ teams unique members, or is there overlap between personnel that might call for mitigation to prevent cross-contamination between sites? Do the site teams have similar compositions in terms of clinical roles and functions or are they highly heterogeneous? In the case of heterogeneity, how will differences between sites be accounted and accommodated for both the intervention and for the usual care comparator? Regarding usual care, the text would benefit from a description of the present standard of care along with usual care practices at each site in order to determine that the randomized groups are not substantively different at baseline. To this point, if the control arm design follow-up plan diverges from usual care in terms of the frequency of clinical follow-up described in the study design, the divergence from usual care should be noted.
Noting the patient eligibility criterion of reduced ejection fraction, it would be appropriate to clarify that the heart failure intervention is specific to heart failure with reduced ejection fraction (HFrEF) and does not encompass care of all patients with heart failure including heart failure with preserved ejection fraction (HFpEF). This clarification would be appropriate throughout the protocol including in the title, as the present depiction of broad heart failure inclusion may be misleading.

Table 3 provides a helpful tool to organize the extensive data collection scheme planned for the study. It is notable that key measures relevant to quality of life assessment including PHQ-9, KCCQ 12, GAD-7, CTM-3, and B-prepared scale are measured only at baseline. These should be measured again at least at the conclusion of the study in order to properly assess the study’s impact on these measures. Similarly, the decision to omit some measures at baseline (e.g. medication adherence scale, specific activity questionnaire, weight management) raises questions about the study’s validity for assessing impact on measures that are not assessed at baseline.

**Study Methods**

The protocol would benefit from additional methodological description of the qualitative interview approach for Aim 1. For example, is the planned sample size of 10-12 interviews for each stakeholder category determined by a grounded theory approach using a semi-structured questionnaire with ongoing analysis until thematic saturation is reached? Is attention paid to key informant characteristics such as geography, socioeconomic status, or other demographic characteristics when composing the sample?

Regarding study measures, the extensive use of validated and reliable tools for Aim 2 is commendable and Table 2 is helpful and well organized. There are some listed items in the table that lack clarity, however. With regard to self-management measures, it is not clear how weight management, diet management, family support, and patient care in depression will be measured. Regarding quality of life, 6-minute walk test is not an appropriate direct measure and should be listed only under walking ability. Regarding functional capacity, more detail is needed about the specific activity questionnaire. Regarding disease severity, detail is needed about the responsiveness to change in heart failure symptoms. Regarding patient satisfaction, more detail is needed about patient satisfaction in quality of care.

Regarding health care expenditure data, significantly more detail is needed about how data will be collected. Will a structured questionnaire be used, and if so will that questionnaire have established validity and reliability? Given the placement of the sentence about health care expenditure data in a paragraph that begins with multimorbidity treatment burden and continues with blood pressure, should it be assumed that this reference to expenditure data will be at the level of the individual patient, and not at the institutional level?

Regarding the description of the study intervention, how will the clinical teams be trained in the intervention? How will fidelity of the intervention be assessed? What is entailed in the mHealth assisted disease management program? Is it a commercially available system? Is it already in use in the target systems? What types of biometrics will it monitor? How does it signal healthcare providers? How does the patient interact with it? Significantly more detail is needed on all of these points.
Regarding Aim 3, the mention of questionnaires that have previously been used in South Asian contexts to assess indirect costs occurred by patients is appreciated and merits more discussion. Do these questionnaires have established validity and reliability? A citation for the questionnaire is needed. In addition, the description of methods for Aim 3 mentions that patients and nurses will be queried about quality of care and other items. Table 4 indicates that investigators will use “in-depth interview.” As with the interviews mentioned for Aim 1, it would be helpful to share more precise information about the qualitative interview methods. Moreover, there may be suitable questionnaires with established validity and reliability to assess some of the items (e.g. quality of care) that may be appropriate to consider. Regarding the additional close-out questionnaire mentioned, more detail is needed about established validity and reliability, along with a citation.

Regarding data analysis, the analytical plan for qualitative data is missing entirely and must be added for both the qualitative interviews planned for Aim 1 and Aim 3.

Is the rationale for, and objectives of, the study clearly described?  
Yes

Is the study design appropriate for the research question?  
Partly

Are sufficient details of the methods provided to allow replication by others?  
No

Are the datasets clearly presented in a useable and accessible format?  
Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Cardiology, implementation science.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 26 Jun 2023

Panniyammakal Jeemon

Thank you for the detailed review and valuable comments on the protocol paper. We have made appropriate corrections in the protocol as suggested. The changes made in the protocol are summarised below.

Rationale for the study:

We have provided the details of one of the missing meta-analyses and cited the article appropriately in the background/introduction section. We have also removed the expansion
We agree that team-based care is inherent to the CCM. However, team-based care with structural changes in the health care delivery mechanism in the LMIC context for management of heart failure is new. We have reorganised the study background section with more focus on the CCM. We have also explained the context in India with additional details in the methodology section. We thank the reviewer for their suggestion to consider RE-AIM framework. Although CCM is reasonably well established in high-income settings, this model with the support of mHealth is not tested in LMIC settings especially among HF patients. We have highlighted this point and focused more on efficacy of our approach than effectiveness. We have used evidence from multiple studies to develop an intervention model that is context specific for India. Further, we utilised the MRC framework for development, implementation, and evaluation of complex public health interventions. Our intervention strategy satisfies the definition of complex public health intervention. We have however, incorporated components of RE-AIM (especially adoption, and maintenance) in the process evaluation. We have added these details in the study design approaches as part of the methods section. We have limitations in further modifying the methodology as it is a funded and ongoing study.

Study design:

Response: In the study design section, we have made the necessary correction as suggested. We appreciate the comments on the inclusion criteria. We are recruiting only heart failure patients with reduced ejection fraction. We have made the corrections in the title and in the protocol text to reflect that the trial is specific to heart failure patients with reduced ejection fraction.

For Aim 1, the number of interviews in the qualitative component will be decided based on the thematic saturation for each stakeholder. We have included stakeholders both from facilities with and without dedicated HF centres. The necessary changes on the rationale for the number of interviews for each stakeholder and the selection of type of stakeholders have been added in the study design section.

For aim 2, the selected units are independent units with dedicated staff employed at each site. Further, the mHealth application would be only available for the selected participant in the study. Therefore, the chance of contamination is minimum. However, patients may get discharged from one hospital and go to another hospital for follow-up care. We would not be able to prevent such cross-over if that happens in the study. However, it will be documented and considered in separate per-protocol analysis if necessary. We have incorporated the description of the units, measures to mitigate the cross-contaminations and handling of heterogeneity across the units in the study design section.

Timing of administration of tools:

We apologise for the oversight, and we have made appropriate changes in table 3 and the manuscript text. The PHQ-9, GAD-7, KCCQ, CTM-3 and B-prepared scale will be repeated at 12-month and 24-month. Some of the measures are not collected at baseline since the
baseline data are collected at discharge after an admission. For example, we may not be able to ask question regarding adherence at the time of discharge. Similarly, some tools are specific for the hospital admission and discharge procedures adopted. It will be administered only during the time of discharge from the hospital. We have separate structured questionnaires for assessing weight management, diet management, family support and patient care in depression. Similarly, specific activity questionnaire, responsiveness to change in heart failure symptoms and patient satisfaction in quality of care are also incorporated as structured questionnaires. We have provided all these tools for data collection in the online supplementary files.

Thank you for identifying the missing citations in Table 2. We have incorporated those missing citations and added them in our reference listing. It was an oversight to include the six-minute walking test along with quality of life. We have made corrections appropriately. The health care expenditure data will be captured using a treatment expenditure questionnaire. It is provided in the online supplement. We have also added the appropriate reference for the questionnaire and cited it in the manuscript text. This tool has been used in the south Asian context for economic evaluation. As noted in the comments, the expenditure data will be measured at the individual patient level and not at the institution level. We have added the details of the mHealth application in the study intervention overview section. The mHealth application is not commercially available. The patient application can be downloaded from Play store but the registration to the application can only be done with the help of the nurse in the project through another application – nurse app. Nurse app is not available in Play store, and it is available to the concerned nurse in the project via invitation. This is to prevent contamination and potential use of the application by other providers and patients.

We thank the reviewer once again for their insightful comments.

**Competing Interests:** None to declare