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Research paper

A randomized controlled trial evaluating a theory driven, complex intervention centered on task sharing and mobile health to improve selfcare and outcomes in heart failure – The PANACEA-HF RCT: Design and rationale

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ABSTRACT

Background: We developed a three-pronged complex intervention to improve selfcare and deliver whole person care for patients with heart failure, underpinned by the 'extant cycle' theory – a theory based on our formative work.

Methods: This is a 3 centre, 2-arm, 1:1, open, adaptive stratified, randomized controlled trial. We included patients aged ≥ 18 years with heart failure, taking any of the key guideline directed medical treatments, with a history of or currently on a high ceiling diuretic. We excluded end stage renal disease, clinically diagnosed severe mental illness or cognitive dysfunction and having no caregivers. Interventions included, (i) trained hospital based lay health worker mediated assessment of patients' current selfcare behaviour, documenting barriers and facilitators and implementing a plan to 'transition' the patient toward optimal selfcare. (ii) m-health mediated remote monitoring and (iii) dose optimization through a 'physician supervisor'.

Results: We recruited 301 patients between Jan 2021 and Jan 2022. Mean age was 59.8 (±11.7) years, with 195 (64.8 %) from rural or semi-urban areas and 67.1 % having intermediate to low health literacy. 190 (63.1 %) had an underlying ischemic cardiomyopathy. In the intervention arm, 142 (94.1 %) had a Selfcare in Heart Failure Index (SCHFI) score of ≤70, with significant barriers being 'lack of knowledge' 105 (34.5 %) and 'behavioural passivity' 23 (7.5 %).

Conclusion: This is the first South Asian trial evaluating a complex intervention underpinned by behaviour change theory for whole person heart failure care. These learnings can be applied to heart failure patient care in other resource constrained health systems.

1. Introduction

The projected annual incidence of heart failure (CHF) in India is 491,000 to 1.8 million [1]. Patients with heart failure in India present at a younger age, are more likely to present in NYHA class IV and have a high co-morbidity and pill burden and are less likely to have medications or health insurance [2]. Studies such as PURE [3] have shown very poor out of hospital adherence to evidence-based treatments, following

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an established stroke or acute myocardial infarction. Though adherence to medications is one among a broader set of behaviours encompassing 'selfcare', we recognize the interrelated and dependent nature of three distinct components necessary to achieving optimal treatment benefits, (i) monitoring – recognizing, correlating and correctly interpreting symptoms and signs by patients and caregivers, (ii) maintenance – adherence to treatments and follow-ups and (iii) management – responding to changing symptoms and signs by generally having a pre-set plan [4]. While treatment guidelines emphasize the importance of attaining the maximally tolerated target doses of recommended medications, they also acknowledge the multiple challenges associated with target dose attainment [5]. Thus, patients who do not follow up regularly with their treating team are at risk of not achieving target doses.

A meta-analysis of self-management interventions in HF that included 20 studies and 5624 individual patients showed that self-management interventions reduced heart failure related hospitalization or all-cause mortality (hazard ratio [HR], 0.80; 95 % CI, 0.71, 0.89), time to heart failure related re-hospitalization (HR, 0.80; 95 % CI, 0.69–0.92) and improved 12-month heart failure related quality of life (standardized mean difference 0.15; 95 % CI, 0.00–0.15) [6]. A systematic review found that the principal drawback of current selfcare intervention programs in chronic diseases is the heterogeneity in intervention content, settings of care, and the mode of delivery, both between studies and within participating centres in a study. A primary underlying factor associated with this heterogeneity is the lack of a theoretical foundation or premise used in the study design phase [7].

We sought to explain selfcare behaviour using a grounded theory approach, analysing interview data from Indian patients with CHF [8,9]. From this, we developed a type of the situation-specific theory of self-care which we call the 'extant cycle' theory. Briefly, we posit that the patient's salient sociocultural background and medical co-morbidities (cognitive dysfunction, mood disorders, others) determine 'extant cycle' elements such as different 'entrenched beliefs', 'behavioural passivity', 'trust issues' or a 'lack of knowledge' that have a reinforcing effect on each other. These in turn impact patients' perceived confidence, motivation and self-efficacy. Patients displaying sub-optimal selfcare behaviour will have an 'extant negative' cycle that needs to be identified during the clinical interaction and appropriate solutions given.

We hypothesized that an intervention package underpinned by the extant cycle theory, comprising a baseline assessment and documentation of the patient's current selfcare behaviour, 'extant cycle' (Appendix 1), barriers and facilitators, structured education and tailored solutions to address barriers, delivered through task sharing and mobile health (m-health) for remote monitoring will improve selfcare and clinical outcomes in patients with chronic heart failure as compared to patients receiving current standard of care. This, to the best of our knowledge is the first study to evaluate a multifaceted intervention directed toward improving selfcare and delivering whole person care, underpinned by a theory of behaviour change among South Asian patients with CHF.

2. Methods

2.1. Study design and ethics statement

We designed a 2-arm, 1:1, open, adaptive stratified, randomized controlled trial. To achieve a balance of important risk predictors affecting selfcare in the 2 arms, we used Pocock's minimisation algorithm, utilizing 5 baseline covariates – age (weighted 10 %) (>75 versus ≤75 years), sex (weighted 10 %), health literacy levels weighted 25 % (high versus low/intermediate), depression (PHQ-9 score < 10 versus 10–19) (weighted 10 %) and recruiting centre (weighted 25 %), with 20 % residual randomness. Embedded in this trial, we will conduct a survey of at least 50 % patients each in the intervention and standard care arm participants to assess intervention acceptability and fidelity, as well as a survey among investigators and the lay health workers.

We obtained the Institutional Ethical Committees (IEC) approvals at all sites (IEC Ref.no. 225/2020, St. John's Medical College Hospital). We obtained written informed consent from all participants, following the Indian Council of Medical Research's (ICMR), National Ethical Guidelines for Biomedical and Health Research involving Human Participants. The trial is registered on the Clinical Trials Registry – India with the reference number CTRI/2021/01/030576 (registered on 01/19/2021).

2.2. Setting

This trial is ongoing at 3 private (non-state funded), non-profit/ charitable, tertiary care hospitals staffed by full time cardiologists and internists. Of these, one (St. John's Medical College. Hospital), is a large non-profit teaching hospital. Patients were recruited from in-patient wards and out-patient departments.

2.3. Eligibility criteria

2.3.1. Inclusion criteria

In both inpatient and outpatient settings, we included patients >/=18 years with a clinical diagnosis of heart failure in NYHA classes I, II or III after stabilization and were either on a RAAS blocker, beta-blocker or vasodilator. Among in-patients, if in NYHA IV, the total daily dose of furosemide (or high ceiling diuretic equivalent) had to be </= 120 mg/day at discharge. Out-patients either had to have a history of having been prescribed or currently on a high ceiling diuretic.

2.3.2. Exclusion criteria

2.3.2.1. In-patients and out-patients. We excluded patients with acute heart failure due to a reversible cause, end-stage renal disease, severe mental illness and severe hemodynamic instability. The exclusion criteria are described in further detail in Table 1.

2.4. Outcome measures

The primary outcome is unplanned heart failure re-hospitalization ***or*** all-cause mortality. Secondary Outcome Measures include, (i) the proportion of all-cause mortality between intervention and control arms; the average days in hospital/ patient/ month in intervention compared to standard care (s.c.) over a 12 month duration; (ii) total heart failure related re-hospitalizations compared between intervention and s.c. groups at 12 months; (iii) time to event analysis of the difference in heart failure rehospitalization or all-cause mortality between two groups; (iv) death due to cardiovascular causes* (definitions in Appendix 2) compared at 12th month; (v) urgent heart failure related outpatient visits compared at 12th month; (vi) general quality of life compared between intervention and control groups at baseline, 1 month, 6 months

Table 1
Detailed exclusion criteria used in PANACEA-HF RCT.

- Patients in acute heart failure with a reversible cause for e.g., heart failure due to thyrotoxicosis or severe anaemia;
- Revascularization and/or Intracardiac Cardioverter Defibrillator (ICD)/Cardiac Resynchronization Therapy (CRT) implantation within 28 days prior to randomization **or** planned in the next two weeks (from screening date);
- Diagnosed with end stage renal disease or requiring renal replacement therapy;
- Hemodynamic instability or shock requiring vasopressors in the current admission.
- Patients with clinically diagnosed severe mental illness such as severe depression or Bipolar Affective Disorder (BPAD);
- Patient Health Questionnaire – 9 (PHQ-9) [10] score of >19 or scoring 1/2/3 on item 9 of the scale ***Or*** scoring 15–19 *and* have no caregivers;
- 6-Cognitive Impairment Test (6-CIT) [11] score > 8 ***and*** have no caregiver.
- Known alcohol dependence or substance abuse with a history of recent binge episodes ***and*** a refusal to commit to quitting and be treated for the same;
- patients who in the opinion of the treating physician have a poor prognosis with predicted survival <12 months and
- an unwillingness to use/ receive any form of m-health intervention.

and 12 months using EQ-5D-5L questionnaire [12]; (vi) change in the selfcare score [17] as measured using the selfcare in heart failure index in the intervention group from baseline to 1 month, 6th month and 12th month respectively; (vii) patients persistence to RAAS blockers including neprilysin inhibitors (ARNi – valsartan + sacubitril) and/or beta-blockers at 1, 6 and 12 months compared between intervention and standard care groups; (viii) change in SCHFI scores in the intervention arm from baseline to 1, 6 and 12 months and (ix) difference in mean SCHFI score at 12th month [13].

All events of mortality and probable cardiovascular/ heart re-hospitalizations will be adjudicated by an independent adjudication committee. All other assessments in the intervention arm - administering SCHFI, EQ-5D-5L, PHQ-9 and 6-CIT scales will be performed by the lay health worker in the intervention arm and by a separate trained study coordinator in the control arm.

3. Intervention arm

3.1. Components of the complex intervention

This is a 3-pronged, multifaceted intervention package involving trained lay health worker centred patient education and imparting selfcare skills; remote monitoring and follow-ups; and optimizing guideline directed medical therapy (GDMT) through a 'physician supervisor'.

3.1.1. Selecting and training the lay health worker

We defined the lay health worker in the context of current trends in the supply of trained healthcare manpower in the Indian healthcare system. A lay health worker is an individual who was either, (i) an individual trained as a 'home health aide', or a 'frontline health worker' under India's National Skill Development Council's (NSDC) Skill India Mission or (ii) at least a 12th grade education with basic writing and speaking skills in English, the Indian vernacular languages and with good communication skills, judged at a 30 min interview by the investigators. Such lay health workers are required to spend at least 80 % of their working hours on the study and their remuneration will be commensurate with this expectation.

They were trained in 3 sessions – 10 days of ward rounds with the cardiology/medicine team where they familiarize themselves with heart failure patients and their care. Then over 5 days they were trained centrally by the national coordinating center. Back at the site over 15 days, under supervision they implemented the intervention package including educating at least 5 patients in heart failure self-care and delivering the quality of life and selfcare questionnaires. The objectives, methods and outcomes of this training are detailed in Appendix 3. Briefly, we trained lay health workers about common cardiovascular risk factors, educated patients on risk factor assessments and management including selfcare and its key components, skills (BP, weight, edema check) and in the use of mHealth modalities. We also trained them on administering various questionnaires, identifying patients with a history of sub-optimal selfcare, barriers/facilitators and goal setting and situating these within the framework of the extant cycle, decision making plan/algorithm on variance/alerts with deranged BP values, weights, plan/algorithm for handling worsening symptoms and signs and plan for dealing with technical problems.

3.1.2. Defining the physician supervisor

The lay health worker is supervised by a physician supervisor. The physician supervisor could be a cardiologist, physician with a post-graduate degree (MD) in internal medicine, community health (or public health) pharmacology or an MBBS qualified doctor/ PharmD with at least 6 months of clinical experience, already employed by the hospital. Personnel with MBBS or PharmD qualifications would need to undergo 3 days training from the national coordinating center and 25 days hands-on training with the cardiology/medicine team at the recruiting center (participating in ward rounds, familiarizing with prescriptions, counselling patients on medications and lifestyle modification) may also be delegated. They also worked up 5 heart failure cases, deploying the intervention package; 2 cases before and 3 after training.

Prong 1 these are interventions delivered primarily through the trained lay health worker, initially supervised by the physician supervisor to achieve improved selfcare monitoring and maintenance. This was delivered at baseline after the patient was randomized into the intervention arm. The health worker educated the patient, demonstrated self-monitoring skills, ascertained barriers to selfcare and prepared and documented a selfcare intervention plan. Importantly, the health workers were trained to deliver two evidence based interventions – (i) patients scoring 5–9 on the PHQ-9 scale, received behavioural activation and relaxation training [14] (patients scoring $\geq$ 10 receive a referral to psychiatry) and (ii) patients at moderate risk from alcohol and/or tobacco received the ASSIST linked brief intervention and those at high risk from alcohol and/or tobacco received the ASSIST linked brief intervention and were referred to a psychiatrist for further management [15] (Detailed in Appendix 5 and 6 respectively).

Prong 2 included remote monitoring, with the health worker serving as the 'nodal point' for triage, escalation to the treating team as needed, and circling back to the patient to support selfcare management. The patients were offered either our in-house built Application (SUHRIDAY), or they would be offered WhatsApp, or they would be actively called by the lay health worker. Patients were advised to send in data daily or at least thrice a week.

Prong 3 addressed medication optimization - closely monitoring patients with initial contraindications to receiving RAAS blockers or beta-blockers at baseline and observing for opportunities to commence these medications quickly. Achieving guideline directed target doses is done over time through close monitoring by the physician supervisor and the treating team. The physician supervisor reviewed doses and key parameters at least once in a month for patients in the intervention group.

All patients in the intervention arm received one standard intervention package (a basic structure), with 'add-on' interventions from a set of 6 'modular' interventions based on every patient's particular need as assessed by the non-physician health worker in consultation with the physician supervisor or treating cardiologist (Table 2). These specific situations include – (i) those with the behaviour trait of passivity; (ii) financially constrained patients (lower-middle, upper-lower or lower socio-economic status or uninsured upper-middle class); (iii) patients with low health literacy and/or entrenched beliefs; (iv) mild cognitive dysfunction; (v) anxiety and/or mild depression; (vi) alcohol or tobacco dependence.

3.1.3. Lay health worker interventions at baseline

Lay health workers assessed and documented patients' age, gender, socio-economic status, health literacy level, social support available and prior medication adherence history and selfcare in patient specific case notes designed for the purposes of this study. Selfcare in the intervention group was assessed using the selfcare in heart failure index (SCHFI). Optimal selfcare is defined as an SCHFI score $\geq$ 70 [13]. Patients assessed to have demonstrated optimal selfcare, were again systematically educated in topics related to heart failure selfcare. All patients and at least one caregiver were trained to recognize and report heart failure symptoms/ signs and skills that included self-monitoring fluid intake using a measuring flask, self-monitoring blood pressure and heart rate using an electronic BP device, measuring and tracking body weight and checking for oedema (why do it, how to do it). Based on their professed financial situation, patients will be offered an electronic BP device (OMRON model no.HEM-8712 AP), a weighing scale (Belita mechanical scale). Patients will be given an easy-to-use structured diary to note the presence or absence of symptoms/ signs and the recorded values.

Table 2
Extant Cycle barriers and their tailored interventions.

Module no	Situation	Intervention
1	Behavioural passivity and obstacle self-perception	(i) Assessing and addressing caregiver's difficulties supporting the patient, (ii) Shared patient-caregiver intervention involving counselling the dyad to set possible goals and shift selfcare tasks from the caregiver to the patient and attempt to complete this process within 30 days; (iii) counselling the patient to take ownership of their health, utilizing various possible facilitators including spiritual faith and cultivating and practising gratitude and a sense of purpose [16].
2	Financially constrained patients	(i) Assessment by the lay health worker and supervising physician at baseline about the extent of financial distress and ability to procure long-term disease modifying treatment, (ii) connecting the patient to applicable state sponsored subsidy or insurance schemes or to charitable organizations and sources of low-cost medications, (iii) referral to medico-social work.
3	Low health literacy. Entrenched beliefs	(i) Counsel patients to procure the same drug brands during prescription re-filling - this helps keep pill morphology constant so patients can 'connect' the pill morphology with the time of day (ii) pill box use (iii) identify a family member who has higher health literacy and is motivated and involve them in the care plan. (iv) address belief systems (v) emphasize the ability of evidence-based medications to improve clinical outcomes and possible benefit long-term family savings.
4	Mild cognitive dysfunction	(i) Caregiver focussed education, (ii) spending more time with kids in the family
5	PHQ9 score 5–9	Lay health worker delivered behavioural activation and relaxation training. [14] (Appendix 5)
	≥10 or 5–9 on 2 consecutive follow-ups	Referral to psychiatry and behavioural training plus relaxation therapy
6	Alcohol and/or Tobacco dependence	ASSIST intervention delivered by lay health worker [15] (Appendix 6)

3.1.4. For patients with an SCHFI score < 70

We have developed a questionnaire, which we call the 'extant cycle determination questionnaire', which is not validated. The domains and items of this questionnaire are described in Appendix 4. This questionnaire is designed to help the lay health worker identify barriers such as behavioural passivity, entrenched beliefs and issues related to trust. Based on the barriers and facilitators identified, the lay health worker creates a customized intervention plan and documents this in the patients' case notes. Based on the barriers, the intervention components could include a combination of the interventions detailed in Table 2.

3.1.5. Remote monitoring - mobile health based remote monitoring

Suhriday is an Android and iOS compatible smartphone application (Appendix 7). The app has a patient interface and a provider interface (also can be viewed on MS-Windows desktop). All consecutive patients opting for remote monitoring are registered on the app with a unique reference number. The basic functions of the app [17] are to facilitate remote monitoring of patients with heart failure – (i) reporting a set of validated symptoms and signs of heart failure [18] daily

- self-monitored blood pressure, heart rate, fluid intake and body weight
- uploading and storing medical records, including transmitting jpeg images of renewed prescriptions
- generating notifications as medication reminders; patients are prompted to swipe across the notification, once they've taken the medications
- an image of the medication blister pack can be taken, which appears alongside the medication notification

3.1.6. Data storage, safety and encryption

Patient data are stored in accordance with applicable guidelines securely and confidentially in Amazon's cloud-based web server.

3.1.7. Triaging and referral through remote monitoring using the Suhriday application

The lay health worker has an Android enabled smartphone with the Suhriday application downloaded. The app alerts the lay health worker to reports of symptom worsening and violation of pre-set parameters for blood pressure, body weight, heart rate and fluid intake. The lay health worker actively monitors for alerts between 9 am to 5 pm. After 5 pm, the patients has been asked to call the lay health worker, if there were to be an emergency (perceived or actual). Once an alert is received by the health worker, she makes a call to the patient. For each symptom/ sign/ clinical parameter, we have developed a brief, structured questionnaire, for the health worker to gather further information. The health worker escalates heart failure or cardiology related alerts to the cardiology team (point of contact – cardiology resident or internal medicine resident on call) with the relevant history and latest key investigation parameters. Issues such as hyperglycaemia or hypoglycaemia, variations in blood pressure or body weight and queries related to lifestyle modification were escalated to the physician supervisor. Escalations and the solutions provided will be documented on an excel file for the health worker to complete and update.

From our prior pilot work [8], we anticipate that patients and families residing in rural areas and those with low health literacy will decline using SUHRIDAY. Hence, we also planned for, (i) **Active structured telephone support** where the lay health worker actively calls up the patient at least thrice a week and administers a structured questionnaire enquiring for symptom exacerbations and measured values (patient notes this in a customized diary). Any warning symptoms or signs picked up by the lay health worker will be appropriately escalated. Advise for resolution will be delivered over the phone (including urgent referrals to hospitals/ physicians) and documented in the nurses log. Such patients will also be counselled to make a telecall to the health worker if there is a worsening of symptoms or signs in the interim periods. (ii) **Through commonly used internet based, voice over-IP, instant messaging service (WhatsApp)** through which photos of the patient diary are sent to the health worker.

3.1.8. Intervention arm follow-ups

Patients were followed up at the 15th day, 3rd month and 9th month post randomization over the telephone and (preferably) at the hospital at months 1, 6 and 12. All follow-ups were in addition to the treating cardiologist/ physician specified follow-ups. A chart of follow-up procedures by time point is given in Appendix 8. Where possible cardiologist specified follow-ups will be synchronized with protocol specified clinic visits. Key activities at these visits included – (i) Physician supervisor reviewed doses of the Angiotensin Converting Enzyme inhibitor (ACEi)/ Angiotensin receptor blocker (ARB)/ Neprilysin Inhibitor (ARNi), beta-blocker and the mineralocorticoid receptor antagonist and coordinated with cardiology/ medicine for possible dose optimization. (ii) Selfcare procedures were reinforced; the SCHFI scale and the EQ-5D-

5L were administered at 1 and 6 months to assess general quality of life. Patient's progress along the extant cycle were assessed, barriers resolved and facilitators reinforced. (iii) Outcome events were recorded along with their documentation and reported side effects of medications were assessed. (iv) Medication persistence to defined medications (RAAS blockers and beta blockers) were enquired into through two questions – (i) Is the patient continuing to take the drug in question? (Yes/No) and (ii) If Yes, in the last one month prior to follow-up, have most doses of the drug been taken or no? (Yes/No).

3.1.9. 12th month final follow-up

At the final follow-up visit, clinical outcomes are being ascertained, selfcare and quality of life scales administered and persistence to medications enquired for. The patients are encouraged to continue optimal selfcare practices.

4. Control arm: standard of care

Present standards of care at most tertiary care hospitals (anecdotal) at discharge and out-patient follow-ups, involves brief advice on lifestyle modification and medication adherence by the cardiologist or internist and reinforcement of this advice, along with dose optimizations at subsequent out-patient follow-ups or discharge following re-hospitalizations. For this trial, we ensured that we selected tertiary care centers staffed by full time cardiologists and internists. The control arm patients are receiving care in accordance with the center's standard of care, where there's a high likelihood of the treating team following guideline directed treatment. At the end of the study, all control arm patients will be educated in selfcare systematically. Patients scoring >/=10 on PHQ-9 will be advised a psychiatry consultation and re-assessed at the 3rd, 6th and 12th month follow-ups with PHQ-9. Patients at high risk from alcohol and/or tobacco will be referred to a psychiatrist for further management (assessed at baseline and 12 months). The SCHFI scale was not administered to the control group at baseline, since elements in the questionnaire may have prompted participants to change their selfcare behaviour, thus diluting possible intervention effects. Instead, we will use an as yet unvalidated 6 item questionnaire with dichotomous responses to assess selfcare in the control arm.

Hospital telephone numbers will be provided for emergency contact. Patients in the standard care group were followed up at 1 month in person to measure – (selfcare, quality of life (EQ-5D-5L), clinical outcomes and medication persistence ascertained), at 3 months by telephone (clinical outcomes, medication persistence), at 6 and 12 months respectively for clinical outcomes, selfcare and quality of life assessment (general quality of life using EQ-5D-5L) and medication persistence.

At the end of 12 months, both intervention and control group patients are educated again about the importance of selfcare. If the m-Health application is in mainstream use at the time, all study participants are given the opportunity of availing the benefits of the intervention. Educational content will be shared with the control group patients as well.

4.1. Sample size estimation

The primary outcome measure for the randomized controlled trial is the proportion of patients having outcomes of unplanned heart failure re-hospitalization or all-cause mortality compared between intervention and standard of care groups at one year [19].

The study is powered to detect a relative risk reduction of 30 % in the intervention arm at 12 months, with a 45 % event-free survival in the control group [20] (two-sided alpha = 0.05, beta 0.80); the required number would be 134 in each arm. After accounting for a dropout rate of 10 %, the required number for the trial in each arm will be 148, so 296 participants are required to be enrolled. We aim to randomize 300 participants in a 1:1 allocation ratio.

4.2. Data management

Study data were collected and managed using REDCap electronic data capture tools hosted at St. John's National Academy of Health Sciences [21,22]. Data were remotely captured on electronic case record forms. Edit checks were built in to capture missing data, outliers and inconsistent data. Customized data quality reports were sent to centres on a quarterly basis. REDCap preserves audit trails for tracking data manipulation and export procedures. Baseline data were exported to 'R' program for statistical analysis [23].

5. Results

We recruited 301 patients meeting eligibility criteria from Jan 24 2021 and Jan 31 2022; patients are currently between 6th and 12th months of follow-up (Fig. 1). Overall, patients have a mean age of 59.8 (±11.7) years and 225 (74.8 %) are male patients (Table 1). 195 (64.8 %) were from semi-urban or rural areas, 202 (67.1 %) having low to intermediate levels of health literacy and 226 (75.1 %) from lower-middle, upper-lower or lower socio-economic strata, all of whom were uninsured. 222 (73.7 %) were recruited from out-patient clinics. 220 (73.1 %) have Heart Failure with reduced ejection fraction (HFrEF) and 26 (8.6 %) HFpEF (definition cut-offs based on ejection fraction).

With 190 (63.1 %) patients, underlying ischemic cardiomyopathy was the predominant etiology for heart failure and 152 (50.5 %) patients had diabetes mellitus as the main risk factor. All prognostic factors were well balanced at baseline (Table 3). 116 (76.8 %) in the intervention arm and 107 (71.3 %) in the control arm received beta-blockers ($p = 0.28$) and 104 (68.9 %) in the intervention arm and 85 (56.7 %) in the control arm received an ACE inhibitor or an ARB ($p = 0.12$), while 24 (15.9 %) and 19 (71.3 %) received an ARNi. Dyspnoea on exertion and fatigue were predominant complaints with 71.1 % and 20.3 % respectively reporting these.

Only 13 (8.6 %) opted to use SUHRIDAY, 72 (47.7 %) said they would note symptoms and monitored values on the patient diary and 66 (43.7 %) opted for active structured telephone support.

6. Discussion

In this trial, we have endeavoured to improve selfcare among patients with chronic heart failure, by delivering an intervention package focussing on patient centred whole-person care. By improving selfcare monitoring, maintenance and management, we hope to reduce risk of mortality and rehospitalization. The intervention is locally contextualized since the intervention components are underpinned by a locally developed theory of behaviour change. It is delivered through a trained lay health worker who can spend more time with patients and deliver interventions, while keeping costs low. We also utilize different forms of mHealth, through which we hope to improve selfcare management. This is a small trial, but significant since it's among the few and first South Asian trials that are evaluating a multi-faceted intervention package underpinned by behaviour change theory to affect an improvement in heart failure selfcare.

The average age of the patients in our trial is younger than Western or Japanese patients, as has been shown by prior large registries [2]. 42 (8.5 %) refused consent during screening, since they did not want to participate in the trial. Importantly, many a time this decision was taken not by the patient, but by a family member, with most being apprehensive of the 'time commitment' needed to participate, despite our counselling that there was no obligation on their part. We have an under-representation of women in the trial (3 in 4 are men). During screening, the investigators noted that the screening failure rate was higher among eligible women, with the dominant men in families sometimes making decisions on their behalf. The reasons for this phenomenon need more investigation, but maybe related to the phenomenon of behavioural passivity that we have priorly described [8].

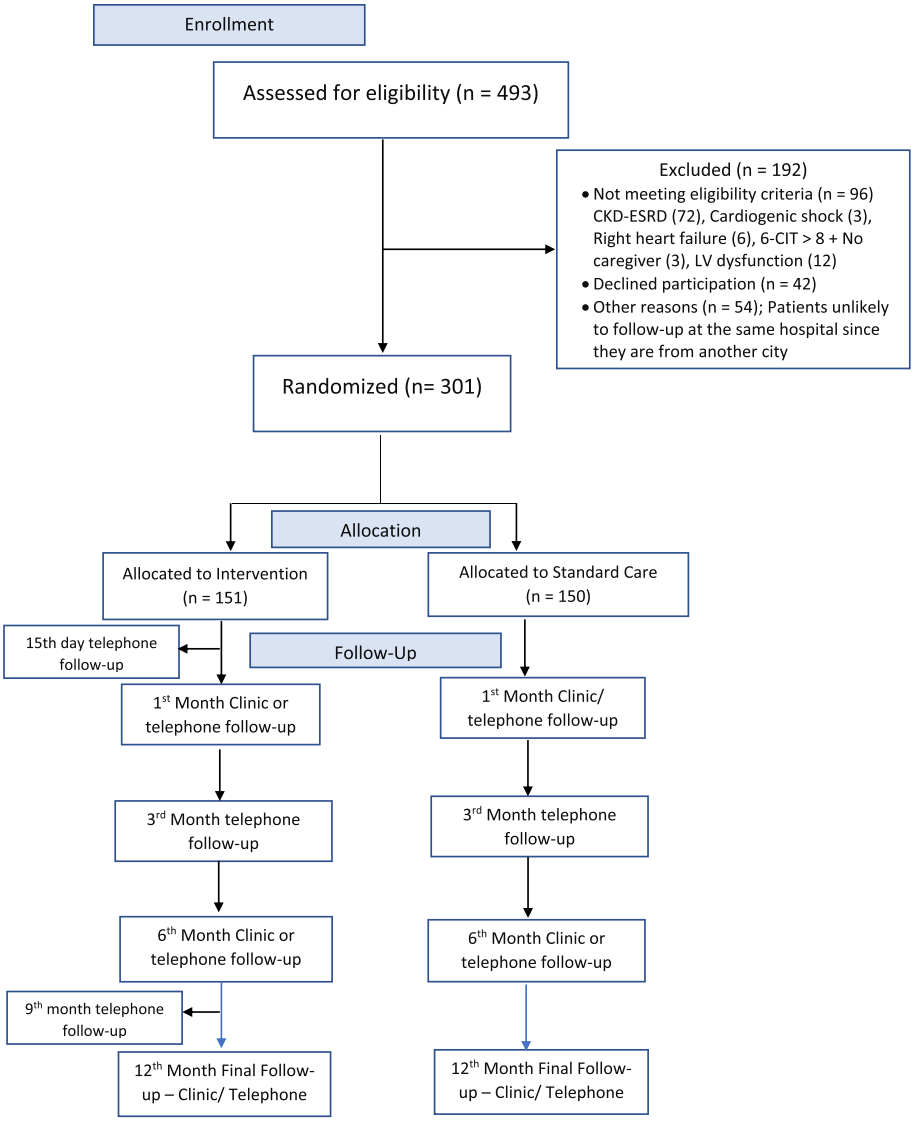

Fig. 1. PANACEA-HF RCT: Study flowchart.

202 (67.1 %) had intermediate to low health literacy levels, while 158 (52.5 %) were from rural areas, living on farmlands with low internet penetration. This explains in part, the reason why patients opted for active structured telephone support over other modalities. Other reasons include patients preference for WhatsApp, due to their confidence using an App they were used to. The third reason is patients recruited from the out-patient department had time constraints (multiple specialty consultations, providing samples to the laboratory and then making the journey back home). By the time the health worker had educated and trained the patients in skills, they had to leave to catch the last train/ bus to their village or hometown.

Our trial is limited by the fact that the assumptions for the control arm event rate and intervention effect size were made from trials that pre-dated the ARNi/SGLT2 inhibitor era and our assumed intervention effects could be overly optimistic. We have limited resources at our disposal for the trial and hence we had a fairly small sample size recruited from three centres. Nonetheless, this trial will provide us with valuable information regarding what components of the intervention package can be implemented through NPHWs in future and what components require a cardiologist, physician or nurse (with special interest in heart disease). We will also analyse fidelity and process change measures that can help us better implement the intervention package when scaling up the trial in future.

7. Conclusion

This trial evaluates a theory driven, complex intervention package that aims to deliver whole person care and improve selfcare, among patients with heart failure. The fact that the intervention is underpinned by a behaviour change theory and utilizes lay health worker and mobile health interventions, makes this a novel intervention in resource limited settings.

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CRediT authorship contribution statement

Deepak Yogesh Kamath: Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Resource Planning, Supervision, Validation,

Table 3
Key demographic and clinical history.

Variables		Overall	Intervention $N = 151$	Control $N = 150$
Age mean (SD)		59.8 (11.7)	60.2 (11.3)	59.5 (12.1)
Gender n (%)	Female	76 (25.2)	38 (25.2)	38 (25.3)
	Male	225 (74.8)	113 (74.8)	112 (74.7)
Residential Zone	Urban	106 (35.3)	55 (36.5)	51 (34.0)
	Semi-urban	37 (12.3)	12 (7.9)	25 (16.7)
	Rural	158 (52.5)	84 (55.6)	74 (49.3)
Socio-economic status	Upper	8 (2.7)	3 (2)	5 (3.3)
	Upper middle	67 (22.3)	35 (23.2)	32 (21.3)
	Lower middle	113 (37.5)	63 (41.7)	50 (33.3)
	Upper lower	78 (25.9)	37 (24.5)	41 (27.3)
	Lower	35 (11.6)	13 (8.6)	22 (14.7)
Patient's health literacy	High	99 (32.9)	48 (31.8)	51 (34)
	Intermediate/low	202 (67.1)	103 (68.2)	99 (66)
Recruitment setting	In-patient	79 (26.3)	37 (12.3)	42 (13.9)
	Out-patient	222 (73.7)	113 (37.5)	109 (36.2)
If out-patient, number of days from discharge of last heart failure hospital admission to randomization	≤30	115 (38.6)	52 (34.7)	63 (42.6)
	31–90	12 (4.0)	6 (4.0)	6 (4.1)
	>90	171 (57.4)	92 (61.3)	79 (53.4)
NYHA Class at recruitment	NYHA 1	83 (27.6)	44 (29.1)	39 (26.0)
	NYHA 2	151 (50.2)	72 (47.7)	79 (52.7)
	NYHA 3	63 (20.9)	33 (21.9)	30 (20)
	NYHA 4	4 (1.3)	2 (1.3)	2 (1.3)
Heart failure type	HFrEF	220 (73.1)	113 (74.8)	107 (71.3)
	HFmrEF	55 (18.3)	21 (13.9)	34 (22.7)
	HFpEF	26 (8.6)	17 (11.3)	9 (6.0)
Primary etiology	Ischemic	190 (63.1)	84 (55.6)	97 (64.7)
	Hypertensive	37 (12.3)	23 (15.2)	14 (9.3)
	Idiopathic Dilated Cardiomyopathy	49 (16.3)	27 (17.9)	22 (14.7)
	Rheumatic valvular disease	2 (0.7)	1 (0.6)	1 (0.6)
	Alcoholic dilated cardiomyopathy	2 (0.7)	1 (0.6)	1 (0.6)
	Others (other valvular, bundle branch blocks, suspected coronary artery disease, myocarditis)	21 (6.9)	14 (9.3)	16 (10.7)
Key risk factors/ comorbid conditions				
Hypertension		126 (41.9)	66 (43.7)	60 (40.0)
Diabetes Mellitus		152 (50.5)	73 (48.3)	79 (52.7)
Smoking	Former	74 (24.6)	36 (23.8)	38 (25.3)
	Current	19 (6.3)	9 (6.0)	10 (6.7)
Stroke		15 (5.0)	9 (6.0)	6 (4.0)
Atrial Fibrillation		18 (6.0)	9 (6.0)	9 (6.0)

Visualization, Writing original draft.

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Denis Xavier: Methodology, Funding Acquisition, Project Administration, Writing Review and Editing.

Ethics statement

We obtained the Institutional Ethical Committees (IEC) approvals at all sites (IEC Ref.no. 225/2020, St. John's Medical College Hospital). We obtained written informed consent from all participants, following the Indian Council of Medical Research's (ICMR), National Ethical Guidelines for Biomedical and Health Research involving Human Participants. The trial is registered on the Clinical Trials Registry – India with the reference number CTRI/2021/01/030576 (registered on 01/19/2021).

Declaration of competing interest

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Appendix A. Supplementary data

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References

[1] M.D. Huffman, D. Prabhakaran, Heart Failure: Epidemiology and Prevention in India, 2010, pp. 283–288.

[2] H. Dokainish, K. Teo, J. Zhu, A. Roy, K.F. Alhabib, A. Elsayed, et al., Heart failure in Africa, Asia, the Middle East and South America: the INTER-CHF study, Int. J. Cardiol. 204 (2016) 133–141.

[3] S. Yusuf, S. Islam, C.K. Chow, S. Rangarajan, G. Dagenais, R. Diaz, et al., Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE study): a prospective epidemiological survey, Lancet 378 (9798) (2011).

[4] A. Stromberg, B.J.T. Riegel, A middle-range theory of self-care of chronic illness, ANS Adv. Nurs. Sci. 35 (3) (2012) 194–204.

[5] P.A. Heidenreich, B. Bozkurt, D. Aguilar, L.A. Allen, J.J. Byun, M.M. Colvin, et al., AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Vol. 145, Circulation 2022, Lippincott Williams and Wilkins, 2022, pp. E895–1032.

[6] B. Riegel, D.K. Moser, H.G. Buck, V.V. Dickson, S.B. Dunbar, C.S. Lee, et al., Self-care for the prevention and management of cardiovascular disease and stroke, J. Am. Heart Assoc. 6 (9) (2017), e006997.

[7] S.R. Toukhsati, T. Jaarsma, A.S. Babu, A. Driscoll, D.L. Hare, Self-care interventions that reduce hospital readmissions in patients with heart failure; towards the identification of change agents, Clin. Med. Insights: Cardiol. (13) (2019), https://doi.org/10.1177/1179546819856855.

[8] D.Y. Kamath, K.B. Bhuvana, L.J. Salazar, K. Varghese, A. Kamath, J. Idiculla, et al., A qualitative, grounded theory exploration of the determinants of self-care behavior among Indian patients with a lived experience of chronic heart failure, PLoS One 16 (2021) (1 January).

[9] D.Y. Kamath, K.B. Bhuvana, R.S. Dhiraj, D. Xavier, K. Varghese, L.J. Salazar, C. B. Granger, P.G.B.B. Pais, Patient and caregiver reported facilitators of self-care among patients with chronic heart failure: report from a formative qualitative study [version 2; peer review: 2 approved with reservations], Wellcome Open Res. 5 (10) (2020).

[10] S. Poongothai, R. Pradeepa, A. Ganesan, V. Mohan, Reliability and validity of a modified PHQ-9 item inventory (PHQ-12) as a screening instrument for assessing depression in Asian Indians (CURES-65), J. Assoc. Phys. India 57 (2) (2009).

[11] A.K. Upadhyaya, M. Rajagopal, T.M. Gale, The six item cognitive impairment test (6-CIT) as a screening test for dementia: comparison with mini-mental state examination (MMSE), Curr. Aging Sci. 3 (2) (2010).

[12] M. Herdman, C. Gudex, A. Lloyd, M. Janssen, P. Kind, D. Parkin, et al., Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L), Qual. Life Res. 20 (10) (2011).

[13] B. Riegel, C.S. Lee, V.V. Dickson, B. Carlson, An update on the self-care of heart failure index, J. Cardiovasc. Nurs. 24 (6) (2009) 485–497.

[14] A. Wenzel, Basic strategies of cognitive behavioral therapy, Psychiatr. Clin. N. Am. 40 (2017).

[15] World Health Organization, Brief Intervention: The ASSIST-Linked Brief Intervention for Hazardous and Harmful Substance Use: Manual for Use in Primary Care, World Health Organization, 2010.

[16] A. Rozanski, Behavioral cardiology, J. Am. Coll. Cardiol. 64 (1) (2014), 100–10.

[17] B.K. Bylappa, D.Y. Kamath, I.S. Josephine, J. Shaikh, A. Kamath, P. Rioniz, S. Kulkarni, K. Varghese, D. Xavier, Usability and feasibility assessment of a smartphone application (Suhriday) for heart failure self-care remote monitoring in an Indian tertiary health care setting: a pilot mixed-methods study, BMJ Open 12 (8) (2022 Aug 24) e056962.

[18] S.I. Chaudhry, B. Barton, J. Mattera, J. Spertus, H.M. Krumholz, Randomized trial of telemonitoring to improve heart failure outcomes (tele-HF): study design, J. Card. Fail. 13 (9) (2007).

[19] N. Sedlar, M. Lainscak, J. Mårtensson, A. Strömberg, T. Jaarsma, J. Farkas, Factors related to self-care behaviours in heart failure: a systematic review of European heart failure self-care behaviour scale studies, Eur. J. Cardiovasc. Nurs. 16 (4) (2017) 272–282.

[20] K.A. Hicks, K.W. Mahaffey, R. Mehran, S.E. Nissen, S.D. Wiviott, B. Dunn, et al., 2017 cardiovascular and stroke endpoint definitions for clinical trials, Circulation 137 (9) (2018).

[21] P.A. Harris, R. Taylor, B.L. Minor, V. Elliott, M. Fernandez, L. O'Neal, et al., The REDCap consortium: building an international community of software platform partners, J. Biomed. Inform. 95 (2019).

[22] P.A. Harris, R. Taylor, R. Thielke, J. Payne, N. Gonzalez, J.G. Conde, Research electronic data capture (REDCap)-A metadata-driven methodology and workflow process for providing translational research informatics support, J. Biomed. Inform. 42 (2) (2009).

[23] Team RC, R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, 2021.