PROTOCOL TITLE: Heart Failure with Reduced Ejection Fraction Polypill in Sri Lanka: A Multi-Center Type I Hybrid Randomized Controlled Trial

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Extramural funds from National Institutes of Health (R00HL157687, PI: Anubha Agarwal), intramural funds from Washington University in St. Louis, and other sources of funds.

ROLES AND RESPONSIBILITIES:
Principal Investigator: Overall leadership of the trial, scientific direction, regulatory oversight, management of collaborating institutions, and communication with DSMB.

Steering Committee: Chaired by the PI and includes senior co-investigators from Sri Lanka, India, Australia, and the United States. Responsibilities include scientific governance through oversight of the trial and key protocol amendments, meets quarterly.

Operations Committee: Includes program managers, study coordinators, biostatisticians, and trial monitors from RemediumOne (Sri Lanka), Washington University in St. Louis (United States), and George Services (India). Oversees day-to-day execution of the trial and responsible for participant recruitment, data entry, monitoring, and site support, meets weekly.

Outcome Adjudication Committee: Includes independent physicians who will adjudicate the primary and other pre-specified outcomes.

Data and Safety Monitoring Board: Independent committee of 5 members with expertise in clinical trials, heart failure, and biostatistics who provide safety oversight by reviewing unblinded data in closed sessions, will meet at pre-specified times based on participant accrual during the trial with ability to convene ad hoc as needed.

STUDY COORDINATING CENTER AND STUDY SITES:
Study coordinating center: Washington University in St. Louis (United States)
Trial implementation in Sri Lanka and oversight of HFrEF polypill manufacturing: RemediumOne (Sri Lanka)
Trial monitoring: George Institute Services India Private Limited
Global academic partners: The George Institute for Global Health, Centre for Chronic Disease Control
Study sites in Sri Lanka: Tertiary care hospitals in Sri Lanka

TRIAL REGISTRATION:

Clinicaltrials.gov NCT07569640
Sri Lanka Clinical Trials Registry

PROTOCOL VERSION NUMBER: 3.0
PROTOCOL VERSION DATE: 22 May 2026

Contents

1. TRIAL SYNOPSIS:

Title	Heart Failure with Reduced Ejection Fraction Polypill in Sri Lanka: A Multi-Center Type I Hybrid Randomized Controlled Trial
Primary objective	Evaluate, in adults with HFrEF in Sri Lanka, the effects of HFrEF polypill-based care on the composite rate of cardiovascular disease mortality and recurrent heart failure hospitalizations, compared with usual care over a minimum of 12-months of follow-up.
Design	Multi-center, parallel group, open-label, type I hybrid randomized controlled trial
Population	Adults ≥18 years with HFrEF (EF ≤40%)
Intervention	HFrEF polypill (over-encapsulated fixed-dose combination) available in 3 strengths: Strength 1: bisoprolol 2.5 mg + losartan 25 mg + eplerenone 25 mg + dapagliflozin 10 mg Strength 2: bisoprolol 5 mg + losartan 50 mg + eplerenone 25 mg + dapagliflozin 10 mg Strength 3: bisoprolol 10 mg + losartan 100 mg + eplerenone 50 mg + dapagliflozin 10 mg
Comparator	Usual care
Primary outcome	1. Composite rate of cardiovascular disease mortality and recurrent heart failure hospitalizations over study duration
Secondary outcomes	1. Rate of cardiovascular disease mortality over study duration 2. Rate of recurrent heart failure hospitalizations over study duration 3. Rate of all-cause mortality over study duration 4. Change in left ventricular ejection fraction at 12-months and end of study assessed by transthoracic echocardiogram 5. Change in BNP levels at 12 months and end of study 6. Change in overall and domain specific health-related quality of life at 12-months and end of study assessed by a translated validated version of the Kansas City Cardiomyopathy Questionnaire (KCCQ-23) 7. Change in physician-reported New York Heart Association class at 12-months and end of study 8. Adherence to guideline-directed medical therapy assessed by pill count and MARS-5 questionnaire at baseline, 1, 6, 12 months, and end of study. Persistence assessed as continuation of assigned therapy at each follow-up visit. Dose optimization assessed as proportion achieving target doses based on local guidelines at 6, 12 months, and end of study.
Safety outcomes	1. Proportion of participants with serious adverse events according to Good Clinical Practice guidelines over study duration 2. Proportion of participants with adverse events of special interest over study duration. These include symptomatic hypotension (SBP <90 mmHg with symptoms), diabetic ketoacidosis, severe hypoglycemia, lower limb amputation, hyperkalemia (K^+ ≥5.5

	mEq/L), and worsening renal function (≥50% increase in serum creatinine or at a lower threshold per physician judgement) 3. Proportion of participants with adverse events leading to HF drug discontinuation over study duration 4. Mean change from baseline to 12-months and end of study in serum potassium (mEq/L) 5. Mean change from baseline to 12-months and end of study in serum creatinine (mg/dL)
Sample size	1,672 randomized.
Statistical considerations	The primary analysis will estimate the treatment effect on the composite rate of cardiovascular disease mortality and recurrent heart failure hospitalizations using the Lin-Wei-Yang-Ying (LWYY) marginal recurrent-events model. Participants will be enrolled continuously during an estimated 18-month accrual period and followed for at least 12 months after randomization, with the entire study concluding 12 months after the final participant is enrolled. Each participant contributes events and follow-up time from randomization until the study end date. This design guarantees a minimum of 12 months of follow-up for all participants while allowing those randomized earlier to contribute longer observation periods, thereby increasing the total number of observable events. The LWYY framework accommodates this variable exposure time by using a robust sandwich variance estimator for recurrent events.
Trial organization	Supported by extramural funds from National Institutes of Health (R00HL157687, PI: Anubha Agarwal) and intramural funds from Washington University in St. Louis, US, and coordinated by Washington University in St. Louis, in collaboration with RemediumOne in Sri Lanka who oversees HFrEF polypill manufacturing and leads implementation of the trial in Sri Lanka. George Institute Services India Private Limited will oversee trial monitoring.

2. BACKGROUND AND RATIONALE

Heart failure is a major global public health problem with the greatest burden in low- and middle-income countries.[1] There is high-quality evidence that guideline-directed medical therapy (GDMT) consisting of 4 medication classes (beta-blockers, renin-angiotensin-system inhibitors, mineralocorticoid receptor antagonists [MRA], and sodium glucose co-transporter 2 inhibitors [SGLT2i]) reduce mortality and morbidity of patients with heart failure with reduced ejection fraction (HFrEF).[2] Suboptimal uptake of GDMT remains a persistent challenge across health systems globally, including in high-income countries, notwithstanding differences in health system capacity and access.[3]

Despite this evidence and inclusion in all major heart failure guidelines, global uptake of GDMT remains low with less than 45% prescribed 3 medication classes, and even fewer prescribed all 4 medication classes including SGLT2i in low- and middle-income countries in a global multinational facility-based heart failure registry.[1,4,5] Community-based estimates are even lower with poor penetration of GDMT, revealing a key target for intervention to improve patient outcomes. Furthermore, the complexity of HFrEF treatment regimens, which commonly involve multiple long-term medications, represents an important barrier to adherence.[6]

Polypills containing 4 GDMT classes in one pill are a promising implementation strategy to bridge this gap between clinical guidelines and practice by addressing multi-level barriers including patient medication adherence, provider clinical inertia, and supply chain complexity.[7] Fixed-dose combination polypills for the prevention of atherosclerotic cardiovascular disease including blood-pressure and lipid-lowering drugs lower the risk of major cardiovascular events and mortality, leading to their inclusion on the World Health Organization's 2023 Essential Medicines List.[8,9] Fixed-dose combination polypills are standard of care for hypertension and recommended in national guidelines.[10] A HFrEF polypill containing quadruple GDMT extends the science and potential benefits of polypills to a new disease condition of HFrEF associated with higher morbidity and mortality.[11] To date, there is no evidence on the effect of HFrEF polypills containing quadruple GDMT on long-term clinical outcomes, particularly in low- and middle-income countries where the burden of heart failure is greatest.

Preliminary studies:

We conducted a multi-center, parallel-group, type 1 hybrid, open-label, pilot randomized controlled trial of a fixed-dose HFrEF polypill containing GDMT (bisoprolol, losartan, eplerenone, and dapagliflozin available in 3 increasing dose strengths) compared to usual care in patients with HFrEF in Sri Lanka.[12] Participants with HFrEF were enrolled from 2 public hospital sites and randomly assigned by a central computer-based service using 1:1 allocation stratified by site. Allocation was fully concealed as no one involved in the conduct of the trial had access to the random allocation sequence at any stage. Researchers, study staff, clinicians, and participants were not blinded to treatment allocation due to the nature of the intervention and comparator (HFrEF polypill vs usual care). The co-primary implementation outcomes were feasibility of recruitment and completion of study-related procedures. Secondary outcomes included adherence to GDMT at 4 weeks measured by pill count and safety. Analyses were per intention to treat. The trial was prospectively registered with the Sri Lanka Clinical Trials Registry (SLCTR/2024/003) and ClinicalTrials.gov (NCT06831864). From January 2025 to May 2025, 43 participants were assessed for eligibility, 3 were ineligible, and 40 randomized with 21 assigned to the HFrEF polypill arm and 19 assigned to usual care arm. The median age of participants was 61 years (interquartile range [IQR] 55-70), 7 (18%) were female, and most participants had ischemic cardiomyopathy (n=35, 88%) with a median left ventricular ejection fraction of 35% (IQR 30%-40%). For the co-primary implementation outcome of feasibility, the overall mean weekly recruitment rate was 6.7 participants/week (SD 2.5) which exceeded our pre-specified target of 4 participants/week. Of those randomized to the HFrEF polypill arm, 21 (100%) received the study drug. Among all randomized participants, 39 (97%) completed 1-week and 4-week follow-up, and 1 (3%) participant withdrew consent. The mean pill count adherence ratio for greater than or equal to 80% adherence to 1 or more medication classes of GDMT based on pill count was 0.85 (SD 0.37) in the HFrEF polypill group compared to 0.47 (SD 0.51) in the usual care group (mean difference 0.38, 95% CI 0.09-0.66, p-value 0.012). There was 1 (5%) serious adverse event in the HFrEF polypill group unrelated to treatment and 2 (11%) serious adverse events in the usual care group due to exacerbation of bronchial asthma and heart failure. In this first pilot randomized controlled trial of a HFrEF polypill in a lower middle-income country, a once-daily, fixed-dose HFrEF polypill containing quadruple

GDMT was a feasible, effective, and safe implementation strategy to improve GDMT rates. These novel proof-of-concept findings support further research on HFrEF polypills to understand longer-term effectiveness on clinical outcomes and tolerability.

3. OBJECTIVES

Evaluate, in adults with HFrEF in Sri Lanka, the effects of HFrEF polypill-based care on the composite rate of cardiovascular disease mortality and recurrent heart failure hospitalizations, compared with usual care over a minimum of 12-months of follow-up.

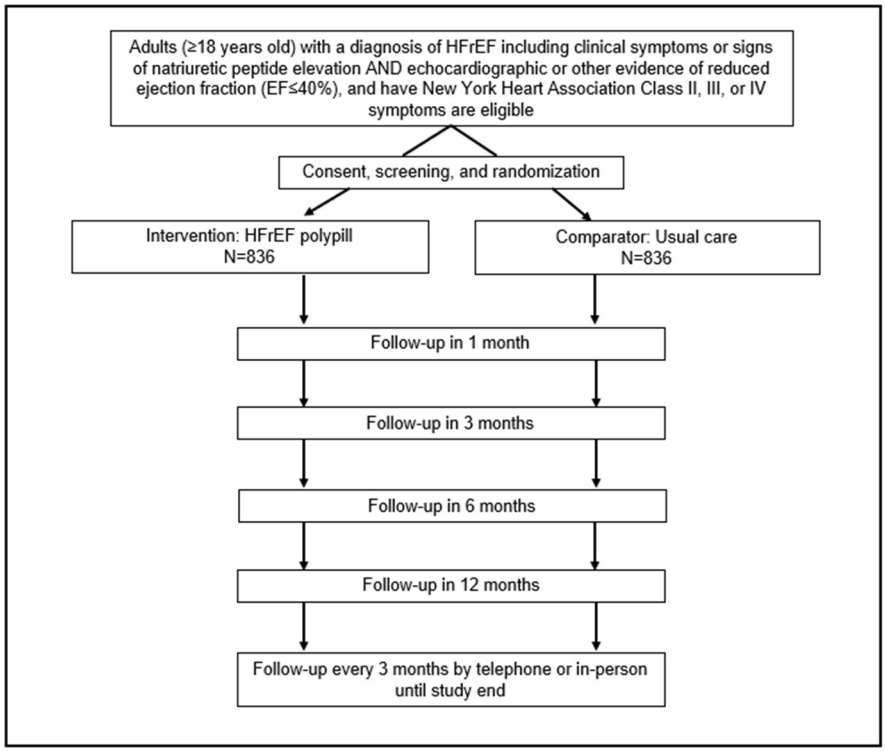
4. STUDY SETTINGS

Tertiary care hospitals in Sri Lanka.

5. STUDY DESIGN

Multi-center, parallel group, open-label, type I hybrid randomized controlled trial

Figure: Design schematic



5.1 RATIONALE FOR STUDY DESIGN

A multi-center, parallel-group, open-label, type I hybrid randomized controlled design was chosen to evaluate the clinical effectiveness of a HFrEF polypill while assessing implementation outcomes relevant to real-world adoption. Randomization ensures internal validity, the multi-center approach enhances generalizability, and the open-label design reflects the pragmatic nature of the intervention. The type I hybrid framework enables timely generation of implementation-relevant evidence alongside clinical outcomes to inform future scale-up.

6. STUDY POPULATION

6.1 Inclusion criteria:

1. Adults (≥18 years old)
2. Diagnosis of heart failure with reduced ejection fraction (HFrEF) including
   a) clinical symptoms or clinical signs or natriuretic peptide elevation AND
   b) echocardiographic or other evidence of reduced left ventricular ejection fraction (EF ≤40%)
3. New York Heart Association Class II, III, or IV symptoms

6.2 Exclusion Criteria:

1. Known contraindication to any of the HFrEF polypill components (e.g., advanced renal disease, bradycardia, allergy, amongst others).
2. Significant renal impairment (estimated glomerular filtration rate <30 mL/min/1.73 m2)
3. Raised serum potassium >5 mEq/L.
4. Symptomatic hypotension or systolic BP <100 mmHg as per the average of last 2 of the 3 measurements at visit 1.
5. Symptomatic bradycardia or second or third-degree heart block without a pacemaker on ECG review at visit 1.
6. History of type 1 diabetes mellitus.
7. Women who are pregnant, breastfeeding or of childbearing potential and are not using and do not plan to continue using a highly acceptable form of contraception throughout the study (pharmacological or barrier methods).
8. Concomitant illness, physical impairment or mental condition which in the opinion of the study team/ primary physician could interfere with the conduct of the study including outcome assessment.
9. Participation in a concurrent interventional medical investigation or pharmacologic clinical trial. Patients in observational, natural history or epidemiological studies not involving an intervention are eligible.
10. Participant's responsible physician believes it is not appropriate for participant to participate in the study.
11. Inability or unwillingness to provide written informed consent.
12. Involvement in the planning and/or conduct of the study.
13. Unable to complete study procedures and/or plan to move out of the study site area in the next 12 months.

This study will not recruit participants from a vulnerable population, including a) individuals who are not yet adults (minors): i.e. infants, children, or teenagers or b) prisoners or other detained individuals.

6.3 Participant recruitment

We will identify patients during hospitalization or routine clinic visits and from a list of potentially eligible participants at each participating site. The study staff will review these potential participants' charts and ensure permission from the patients' treating physician, if necessary, to contact for potential participation in the study. If patients express interest (either during contact when hospitalized, in outpatient clinic, or by telephone), then the screening visit will be scheduled (either during hospitalization immediately prior to discharge, during outpatient clinic, or a separate clinic appointment). During the screening visit, the study team will obtain informed consent and conduct baseline assessments to determine eligibility status. Eligible participants will be randomized.

7. STUDY INTERVENTION AND COMPARATOR

7.1 Intervention:

The study intervention will be a HFrEF polypill consisting of bisoprolol (beta-blocker), losartan (ARB), eplerenone (MRA), and dapagliflozin (SGLT2i) manufactured using the over-encapsulation method and will undergo stability testing to ensure quality. There will be 3 strengths of the HFrEF polypill available to facilitate initiation with low dose to prioritize clinical tolerability and laboratory safety and titration to higher doses of the HFrEF polypill.

HFrEF polypill strengths:
Strength 1: bisoprolol 2.5 mg + losartan 25 mg + eplerenone 25 mg + dapagliflozin 10 mg
Strength 2: bisoprolol 5 mg + losartan 50 mg + eplerenone 25 mg + dapagliflozin 10 mg
Strength 3: bisoprolol 10 mg + losartan 100 mg + eplerenone 50 mg + dapagliflozin 10 mg

The dose of initiation and titration will be at the investigator's discretion, guided by an initiation and titration protocol. The HFrEF polypill will be prescribed by licensed physicians responsible for managing heart failure at participating sites. Eligible providers must have formal medical qualifications in Sri Lanka and be actively involved in the care of patients with HFrEF. This includes cardiologists, internists, or general practitioners with experience in heart failure management. Participants will receive HFrEF polypill free of cost. Participants receiving the HFrEF polypill will also receive a "HFrEF polypill card" that delineates the drugs and doses included in the HFrEF polypill and contact information for the local study team in case of hospitalization at another facility.

7.2 Comparator:

Participants in the comparator control group will receive usual care from their healthcare providers. Providers will be encouraged to treat all participants according to international and local clinical practice guidelines. Participants will receive their HFrEF medications through the pharmacy at the sites where they are usually free of cost. Participants will receive a "trial card" that includes contact information for the local study team in case of hospitalization at another facility.

8. STUDY ENDPOINTS

Primary outcome:
1. Composite rate of cardiovascular disease mortality and recurrent heart failure hospitalizations over study duration

- Cardiovascular disease mortality is defined as death due to acute myocardial infarction, worsening heart failure, stroke, sudden cardiac death, arrhythmia, pulmonary embolism, cardiovascular procedures or their complications, other vascular causes, or any death of unknown cause unless a non-cardiovascular etiology is clearly established.
- HF hospitalization is defined as any unplanned hospitalization for at least 24 hours, for which the primary cause is heart failure, accompanied by objective evidence of decompensation and requiring initiation or intensification of HF-specific therapy, occurring after a documented period of clinical stability of at least 12 hours since the prior HF event.
- Assessed throughout the study and specifically at 1-month, 3-month, 6-month, 9-month, and 12-month study visits and thereafter, every 3 months by telephone or in-person until study end using structured questionnaires.
- Adjudicated by the blinded Outcome Adjudication Committee.

Secondary outcomes:

1. Rate of cardiovascular disease mortality over study duration
   - Cardiovascular disease mortality is defined as death due to acute myocardial infarction, worsening heart failure, stroke, sudden cardiac death, arrhythmia, pulmonary embolism, cardiovascular procedures or their complications, other vascular causes, or any death of unknown cause unless a non-cardiovascular etiology is clearly established.
   - Assessed throughout the study and specifically at 1-month, 3-month, 6-month, 9-month, and 12-month study visits and thereafter, every 3 months by telephone or in-person until study ends using structured questionnaires.
   - Adjudicated by the blinded Outcome Adjudication Committee.

2. Rate of recurrent heart failure hospitalizations over the study duration
   - HF hospitalization is defined as any unplanned hospitalization for at least 24 hours, for which the primary cause is heart failure, accompanied by objective evidence of decompensation and requiring initiation or intensification of HF-specific therapy, occurring after a documented period of clinical stability of at least 12 hours since the prior HF event.
   - Assessed throughout the study and specifically at 1-month, 3-month, 6-month, 9-month, and 12-month study visits and thereafter, every 3 months by telephone or in-person until study ends using structured questionnaires.
   - Adjudicated by the blinded Outcome Adjudication Committee.

3. Rate of all-cause mortality over the study duration
   - All-cause mortality is defined as death due to any cause.
   - Assessed throughout the study and specifically at 1-month, 3-month, 6-month, 9-month, and 12-month study visits and thereafter, every 3 months by telephone or in-person until study end using structured questionnaires.

4. Change in left ventricular ejection fraction at 12-months and end of study assessed by transthoracic echocardiogram
   - Assessed at baseline, 12-months and end of study.

5. Change in BNP levels at 12 months and end of study
   - Assessed at baseline, 12-months, and end of study using a validated commercially available immunoassay, with analyses conducted at a central or certified local laboratory according to site capacity according to standard protocol.

6. Change in overall and domain specific health-related quality of life at 12-months and end of study assessed by a translated validated version of the Kansas City Cardiomyopathy Questionnaire (KCCQ-23)
   - Assessed at baseline, 12-months and end of study.

7. Change in physician-reported New York Heart Association class at 12-months and end of study
   - Assessed at baseline, 12-months and end of study.

8. Adherence to guideline-directed medical therapy assessed by pill count and MARS-5 questionnaire at baseline, 1-, 6-, 12-months, and end of study. Persistence assessed as continuation of assigned therapy at each follow-up visit. Dose optimization assessed as proportion achieving target doses based on local guidelines at 6-, 12-months, and end of study.
   - Assessed at baseline, 1-, 6-, 12-months and end of study.

<u>Safety outcomes:</u>

1. Proportion of participants with serious adverse events according to Good Clinical Practice guidelines over study duration
   - Assessed throughout the study and specifically at 1-month, 3-month, 6-month, 9-month, and 12-month study visits and thereafter, every 3 months by telephone or in-person until study end using structured questionnaires.

2. Proportion of participants with adverse events of special interest over study duration
   - Adverse events of special interest are defined as:
     a) symptomatic hypotension: systolic blood pressure <90 mmHg and associated symptoms (e.g., light-headedness, pre-syncope)
     b) diabetic ketoacidosis: presence of ketosis (blood β-hydroxybutyrate ≥3.0 mmol/L or moderate–large urine ketones) together with metabolic acidosis (arterial or venous pH <7.30 and serum bicarbonate <18 mmol/L), with or without hyperglycaemia (plasma glucose ≥250 mg/dL)
     c) severe hypoglycemia: hypoglycaemia requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.
     d) lower limb amputation: surgical removal of any part of the lower extremity at or proximal to the ankle joint, performed for vascular, infectious, or diabetic complications, excluding minor traumatic injuries or elective cosmetic procedures.
     e) hyperkalemia: serum potassium greater than or equal to 5.5 mEq/L,
     f) worsening renal function: ≥50% increase in serum creatinine or at a lower threshold per physician judgement.
   - Assessed throughout the study and specifically at 1-month, 3-month, 6-month, 9-month, and 12-month study visits and thereafter, every 3 months by telephone or in-person until study end using structured questionnaires.

3. Proportion of participants with adverse events leading to HF drug discontinuation over study duration
   - Assessed throughout the study and specifically at 1-month, 3-month, 6-month, 9-month, and 12-month study visits and thereafter, every 3 months by telephone or in-person until study end using structured questionnaires.

4. Mean change from baseline to 12-months and end of study in serum potassium (mEq/L)
   - Assessed at baseline, 1-month, 3-month, 6-month, 9-month, 12-month, and end of study visits.

5. Mean change from baseline to 12-months and end of study in serum creatinine (mg/dL)
   - Assessed at baseline, 1-month, 3-month, 6-month, 9-month, and 12-month study visits, and end of study visits.

9. STUDY PROCEDURES

Participants with HFrEF will be recruited from inpatient departments prior to hospital discharge or from outpatient departments. Once enrolled and after a baseline visit, participants will complete 1-month, 3-month, 6-month, 9-month and 12-month study visits and thereafter, every 3 months by telephone or in-person until study end to assess outcomes (**Table 1**).

9.1 ASSESSMENT PROCEDURES

All study assessments will be performed according to standardized procedures as outlined in the study Manual of Procedures. Vital signs, including blood pressure, heart rate, and weight, will be measured at study visits by trained study personnel using calibrated equipment following a standardized protocol. Laboratory investigations (including serum electrolytes, creatinine, eGFR, and natriuretic peptides) will be performed and analyzed at a central or certified local laboratory according to site capacity in Sri Lanka according to standard

protocols and quality control procedures. Electrocardiograms and transthoracic echocardiograms will be conducted and interpreted by qualified personnel using standard clinical protocols. Patient-reported outcomes, including the Kansas City Cardiomyopathy Questionnaire and medication adherence assessments, will be administered by trained staff. Detailed procedures for all assessments, including timing, measurement techniques, and data recording, are described in the study Manual of Procedures.

9.2 Visit schedule and assessments

Table 1. Study Visit Activities

Visit	**Screening (V1)**	**Randomization (V2)**	**1 Month (V3)**	**3 Month (V4)**	**6 Month (V5)**	**9 Month (V6)**	**Month 12 (V7)**	**Every 3 months until study end (V8 +)**	**EOS**
Day	**Day -15 to 1**	**Day 1**	**Day 28 ± 7**	**Day 90 ± 14**	**Day 180 ± 14**	**Day 270 ± 14**	**Day 360 ± 14**	**After Day 360, Every 90 ± 14 days**	**EOS**
Informed consent	X								
Eligibility assessment	X	X							
Demographics and medical history	X								
Vital signs (BP, HR, weight)	X		X	X	X	X	X		X
Labs: Serum potassium	X		X	X	X	X	X		X
Labs: Serum creatinine	X		X	X	X	X	X		X
Labs: eGFR	X		X[a]	X[a]	X[a]	X[a]	X[a]		
Labs: Serum sodium	X		X	X	X	X	X		X
Labs: BNP	X						X		X
Labs: Pregnancy test for women of childbearing potential	X		X[b]	X[b]	X[b]	X[b]	X[b]		
ECG/Interpret ECG	X								
Transthoracic echocardiogram (LVEF assessment)[C]	X						X		X
Randomization		X							
Dispense study drug (HFrEF polypills)		X	X	X	X	X	X	X	
HFrEF polypill titration decision (per protocol)			X	X	X	X	X		

GDMT reconciliation and pill count of HFrEF polypill or individual GDMT			X		x		X		X
Assessment of discontinuation of HFrEF polypill or individual GDMT			X	X	X	X	X		
Assessment of CVD mortality			X	X	X	X	X	X	X
Assessment of HF hospitalizations			X	X	X	X	X	X	X
Assessment of all-cause mortality			X	X	X	X	X	X	X
KCCQ	X						X		X
NYHA functional class	X						X		X
Assessment of adverse events/AESI/SAE			X	X	X	X	X	X	X
MARS-5 adherence questionnaire			X	X	X	X	X		X
Concomitant medications	X	X	X	X	X	X	X		X
Confirm contact information for study retention	X	X	X	X	X	X	X	X	

a- eGFR results required at screening. At follow-up, to be recorded if available only.
b- Urine pregnancy test done at screening. If determined required by the investigator, will be done at follow-up as well.
c- Echo reports within 6 months of screening can be considered.

AE: Adverse Event; BP: Blood Pressure; CVD: Cardiovascular Disease; ECG: Electrocardiogram; GCP: Good Clinical Practice; GDMT: Guideline-Directed Medical Therapy; HF: Heart Failure; HFrEF: Heart Failure with Reduced Ejection Fraction; HR: Heart Rate; KCCQ-23: Kansas City Cardiomyopathy Questionnaire (23-item); LVEF: Left Ventricular Ejection Fraction; MARS-5: Medication Adherence Report Scale (5-item); BNP: B-type Natriuretic Peptide; NYHA: New York Heart Association

10. SAMPLE SIZE AND STATISTICAL CONSIDERATIONS

10.1 Sample size

The target sample size is 1,672 participants (836 per arm), calculated using the Lin-Wei-Yang-Ying (LWYY) method for recurrent event analysis, which accounts for within-subject correlation of events and heterogeneity in recurrence rates. The calculation assumes a control arm annual event rate of 30% for the composite of cardiovascular death and recurrent heart failure hospitalizations. This estimate mirrors other heart failure trials (CHARM-Alternative: 40% over 34 months; EMPHASIS-HF: 25.9% over 21 months; PARADIGM-HF: 26.5% over 27 months; DAPA-HF and EMPEROR-Reduced: 21.2% and 24.7% respectively). In Indian cohorts such as the National Heart Failure Registry (NHFR), the 1-year all-cause mortality rate was 22.1% and 1-year readmission rate approximately 8–10%, supporting a combined annual CV death or HF hospitalization incidence near 30% in real-world settings.

The expected treatment effect corresponds to a rate ratio of 0.71 (29% relative risk reduction), representing the average treatment effect across multiple heart failure drug classes for the composite endpoint. Using a two-sided significance level of $\alpha = 0.05$ and targeting 80% power, the base calculation yields 1,505 participants after incorporating a dispersion factor ($\varphi = 1.4$) to account for within-participant variability. Inflating this estimate by 10% for loss to follow-up yields a final target enrollment of 1,672 participants.

10.2 Summary of the statistical analysis plan

The primary outcome analysis will estimate the treatment effect on the composite rate of cardiovascular disease mortality and recurrent heart failure hospitalizations using the LWYY model for recurrent events. This approach uses generalized estimating equations to estimate the rate ratio comparing the HFrEF polypill group to usual care, while accounting for within-subject correlation of recurrent events through a robust sandwich variance estimator. Participants will contribute events and person-time from randomization until the earliest of cardiovascular death (terminal event), withdrawal of consent, loss to follow-up, or study end. The model will be adjusted for randomization stratification variables (site and sex) and relevant baseline covariates to improve precision. Sensitivity analyses will include time-to-first-event Cox regression and win ratio analysis. Win ratio analysis will compare all possible pairs of participants (one from each treatment group) based on a priority sequence of outcomes: first cardiovascular death (with earlier death representing a loss), then total heart failure hospitalizations (with more hospitalizations representing a loss), then time to first heart failure hospitalization. We will then calculate the ratio of pairs won by the polypill group to pairs won by the usual care group). All efficacy analyses will use the intention-to-treat population as the primary analysis population.

Secondary outcomes will be analyzed using methods appropriate to each outcome type. Cardiovascular mortality and all-cause mortality will be analyzed using Cox proportional hazards regression adjusted for stratification variables and baseline covariates, with testing of the proportional hazards assumption along with Kaplan-Meier survival curves, log-rank tests. The rate of recurrent heart failure hospitalizations will be analyzed using the LWYY model identical to the primary outcome methodology, with all-cause death serving as a terminal event. As a pre-specified sensitivity analysis, time to first heart failure hospitalization will be analyzed using Cox proportional hazards regression with Kaplan-Meier survival curves. Change in left ventricular ejection fraction, BNP levels and overall and domain-specific Kansas City Cardiomyopathy Questionnaire (KCCQ-23) scores at 12 months will be analyzed using analysis of covariance (ANCOVA) with adjustment for corresponding baseline values, stratification variables, and relevant covariates. For the KCCQ, analyses will evaluate proportions achieving clinically meaningful improvement (≥5-point increase). Change in physician-reported NYHA functional class at 12 months will be analyzed using ordinal logistic regression. Adherence measures (pill count and MARS-5 scores) will be analyzed using mixed-effects models to account for repeated measures, with treatment group, time, and treatment-by-time interaction as fixed effects. Persistence (continuation of assigned therapy) will be analyzed using Kaplan-Meier methods and Cox

regression for time to treatment discontinuation. Dose optimization (proportion achieving target doses at 6 and 12 months) will be analyzed using log-binomial or modified Poisson regression with robust variance estimation.

Safety outcomes will be summarized as proportions with 95% confidence intervals and compared between groups using risk ratios. Mean changes in serum potassium and creatinine will be analyzed using ANCOVA adjusted for baseline values, stratification variables, and baseline covariates.

Exploratory subgroup analyses will be conducted to assess treatment effect heterogeneity across key demographic and clinical characteristics, including age, sex, disease severity, and comorbidities. To account for multiple comparisons, appropriate statistical procedures will be used to control the family-wise Type I error rate across the primary and key secondary outcomes. Missing data and patterns of missingness will be summarized by treatment group and time point. The primary composite outcome and its components will account for censoring due to loss to follow-up, withdrawal, or administrative study end. Sensitivity analyses, including complete-case analyses and alternative assumptions where appropriate, will be conducted to assess the robustness of results to missing data.

10.3 Interim analyses

The Data Safety and Monitoring Plan (DSMP) documents the provisions to monitor the data and ensure safety of all study participants. The DSMB will review unblinded descriptive data at approximately the mid-point of the trial in a closed session, and will have authority to recommend early termination of the trial for any concerns. The DSMB may also convene ad hoc meetings if suspected unexpected serious adverse reactions or other urgent safety concerns arise. Decisions regarding early termination for futility or safety will be based on observed treatment effects, safety signals, event accrual, and overall study conduct. The DSMB will provide recommendations to the study team regarding continuation, modification, or termination of the trial.

11. RANDOMIZATION AND BLINDING

Allocation ratio

Participants will be randomized in a 1:1 ratio to receive either the HFrEF polypill (intervention arm) or usual care (comparator arm).

Randomization method

Randomization will be performed centrally using the REDCap randomization module with a computer-generated random allocation sequence. Randomization will be stratified by study site and sex using variable block sizes to maintain allocation concealment.

Allocation concealment

Allocation will be fully concealed. Study staff responsible for participant enrollment will not have access to the randomization sequence prior to assignment. Treatment allocation will be revealed only after participant enrollment and completion of baseline assessments.

Blinding and unblinding procedures

This is an open-label trial due to the nature of the HFrEF polypill intervention and the control i.e. usual care. Participants and treating clinicians will be aware of treatment assignment. However, the Outcome Adjudication Committee will remain blinded to treatment allocation. Unblinding for safety reasons will occur only if deemed necessary by the DSMB.

12. DATA COLLECTION AND MANAGEMENT

Data will be collected on paper CRFs and entered into a REDCap database (eCRF) hosted at Washington University in St. Louis within five business days of collection. REDCap provides role-based access

controls, audit trails, secure data transmission, and storage compliant with U.S. 21 CFR Part 11 and HIPAA regulations and applicable Sri Lankan data protection requirements. Participant data will be identified only by a unique study identification number. A separate linkage file connecting study IDs to personally identifiable information will be stored securely at sites in Sri Lanka, and access to identifiable data will be restricted to authorized study personnel. Only approved study staff will have access to the eCRF and electronic database. We will restrict export rights to the study biostatistician only. All exports will be housed in secure directories with restricted access. Our Data and Safety Monitoring Plans and Data Management Plans outline details on data and safety monitoring and quality checks. Blood samples collected for this study will only be used for this study and will be destroyed after testing as per local regulatory guidelines. The study staff will retain all study records required by applicable regulatory bodies in a secure and safe facility for a period recommended by the local ethics committee. Access to study records will be limited to study team members, unless through written application to and approval by the study Steering Committee.

13. DATA SAFETY AND MONITORING PLAN

The Data Safety and Monitoring Plan (DSMP) documents in detail the provisions to monitor the data and ensure safety of all study participants. Briefly, (1) we will convene an independent Data Safety and Monitoring Board (DSMB) consisting of 5 members with diverse backgrounds and fields of expertise, (2) the DSMB will meet at the beginning and other pre-specified times based on participant accrual during the trial with ability to convene ad hoc as needed including if there was a suspected unexpected serious adverse reaction (SUSAR) to review safety and essential study data; (3) we will employ centralized monitoring approaches to monitor data quality and safety; (4) we will program an email alert to study staff in the event of an SAE; we will adhere to regulatory requirements for expedited AE / SAE reporting and referral for additional care if needed.

14. SAFETY MONITORING

Adverse events will be systematically assessed as one of the study outcomes using predefined clinical criteria. Each adverse event will be defined and measured through structured clinical evaluations, laboratory investigations, and patient interviews using standardized forms. The primary metric will be the incidence of specific adverse events, aggregated as the proportion of participants experiencing ≥1 adverse event, and analyzed at 1, 3, 6, 9, 12 months, and until study end for participants remaining in the study. Assessments will be performed by trained study personnel or by treating physicians who are not blinded to treatment allocation due to the nature of the intervention. All SAEs will be promptly reported to the sponsor, Institutional Review Board (IRB), Data and Safety Monitoring Board (DSMB), and regulatory authorities in accordance with local and international reporting requirements.

14.1 ADVERSE EVENT ASSESSMENT AND REPORTING

Adverse events will be assessed for severity and relatedness to study treatment by the site investigator in accordance with International Council for Harmonisation (ICH) Good Clinical Practice guidelines. Severity will be graded as mild, moderate, or severe, and causality will be categorized as related, possibly related, or unrelated to the study intervention. Suspected unexpected serious adverse reactions (SUSARs) will be identified based on seriousness, unexpectedness, and reasonable causal relationship to the study drug and will be reported to the sponsor, DSMB, Institutional Review Board, and relevant regulatory authorities in accordance with local and international expedited reporting requirements.

Pregnancies occurring during the study will be reported promptly as adverse events of special interest and followed through pregnancy outcome. Study drug will be discontinued immediately upon confirmation of pregnancy, and appropriate clinical follow-up will be ensured.

Principles of stopping or modification criteria that will be specified by the DSMB include:

- Excess serious adverse events in the intervention group
- Unexpected safety signals related to the HFrEF polypill
- Evidence that continuation would pose unacceptable risk to participants

15. ETHICS, PROTOCOL AMENDMENTS, CONSENT PROCESS

This study will be conducted in accordance with the principles of the Declaration of Helsinki**,** ICH-GCP guidelines, and all applicable local regulations.

Ethical approval will be obtained from:

- Washington University in St. Louis Institutional Review Board (United States)
- National Medicines Regulatory Authority of Sri Lanka (Sri Lanka)
- University of Kelaniya Ethics Review Committee (Sri Lanka)
- Approval from the University of Kelaniya Ethics Review Committee will serve as the central ethics approval for the study and will apply to all participating trial sites.

Written informed consent will be obtained from all participants prior to study procedures. Consent forms will be available in English, Sinhala, and Tamil**.** The study staff will elicit consent from participants at the hospital site during hospitalization or outpatient clinic visit. Ample time will be devoted to the consent process. Participants will be allowed time to consider the trial and ask questions and will be reminded they are free to leave the trial at any time. Prior to enrollment, participant consent and understanding of the trial will be confirmed. For participants with limited literacy, the consent process will be conducted verbally in their preferred language, with the presence of an impartial witness. The study staff will read the consent form aloud, explain all elements of participation, and address any questions or concerns. The witness will confirm that the participant understands the information provided and freely consents to participate, with consent documented via thumbprint and witness signature. Participants may withdraw from the study at any time without penalty or loss of standard medical care.

16. RISK AND BENEFITS TO PARTICIPANTS

Participants may experience risks related to heart failure pharmacotherapy, including hypotension, electrolyte disturbances, renal dysfunction, and other known medication-related adverse effects. These risks will be mitigated through careful participant selection, protocol-guided dosing and titration, and ongoing safety monitoring. Potential benefits include improved adherence to guideline-directed medical therapy, reduced treatment complexity, and enhanced clinical monitoring, which may improve symptoms and health status. Individual participants in the usual care group may not experience direct benefit. The study may generate important evidence to inform future strategies for optimizing heart failure care.

17. QUALITY MANAGEMENT AND MONITORING

All participating physicians will receive standardized training on the study protocol including initiation and titration protocol, HFrEF polypill composition, and guidance for patient counseling prior to trial initiation to ensure consistent and accurate delivery of the intervention.

Quality assurance will be ensured through a combination of:

- Central statistical monitoring including weekly data safety and quality reports reviewed by the operations committee.
- On-site and remote monitoring by George Services India
- Routine data quality checks and query resolution reviewed weekly by the operations committee.
- Standard operating procedures for protocol adherence.

Protocol deviations and violations will be documented, reviewed, and reported according to regulatory requirements. Corrective and preventive actions (CAPA) will be implemented as needed.

18. STUDY DRUG SUPPLY AND STORAGE

All HFrEF polypills will be packaged, labeled, and distributed by the licensed pharmaceutical manufacturing partner. All HFrEF polypill inventory will be labeled as per local regulatory requirements.

Quantity of Study Drug Dispensed

The study team and licensed pharmaceutical manufacturing partner maintain accountability for each dose of HFrEF polypill it receives, dispenses, disposes, transfers to site, or returns. Each intervention participant's individual drug kit will contain 1 bottle with 35 polypills of the study drug. Bottles dispensed will be based off the number of days between visits with one polypill per day for that time period included. Study staff will make every effort to have participants return for their follow-up visits within the window period at 1-month, 3-month, 6-month, 9-month and 12-months (and subsequently every 3 months for participants remaining in the study beyond the 12-month study visit). This will ensure participants do not run out of their HFrEF polypill. Study staff will aim to synchronize follow-up visits with the patient's regular appointment for patient convenience.

Dispensing Directly to Participants

Once the study staff member obtains a participant's information from REDCap (after randomization), he / she will complete an outpatient Investigational Drug Order Form (IDOF), which is the written order for the investigational drug that includes the protocol number, patient study number, and study drug number. The IDOF must be signed by the local site investigator, or other authorized physician investigator.

Drug Accountability

Drug accountability at the participant level will be monitored centrally through completion of the eCRF: Study Start Form and generation of reports for this form. Participant-level accountability will be monitored via participant listings in conjunction with an on-site monitoring visit. Drug accountability will be verified for 100% of enrolled participants; any discrepancies / queries / violations at the participant level will be noted.

Disposal and Destruction

All returned drug products and containers will be housed at the study site in a designated area or shelf within the storage closet. After drug accountability procedures have been completed by the monitor for these drug kits, unused products will be destroyed at the site or returned to pharmaceutical manufacturing partner for destruction.

19. DATA AND SPECIMEN BANKING

Blood samples collected for routine clinical laboratory assessments will be processed and analyzed at a central or certified local laboratory according to site capacity in Sri Lanka according to standard protocols. Biological specimens will not be stored for future unspecified research. All samples will be destroyed after completion of the planned laboratory analyses per local procedures.

Study data will be retained for a minimum of 7 years following study completion or longer if required by regulatory authorities or institutional policies. De-identified analytic datasets may be archived on secure institutional servers at Washington University in St. Louis consistent with NIH data-sharing policies.

20. SHARING RESULTS WITH PARTICIPANTS

Participants will be informed of the overall study results through multiple mechanisms. At the conclusion of the trial and following publication of the primary results, a lay summary describing the study objectives, methods, and key findings will be developed in English, Sinhala, and Tamil**.** This summary will be shared with participants during routine clinic visits, by telephone, or via text message, depending on participant preference and feasibility.

Individual clinical results relevant to participant safety (e.g., abnormal laboratory values or echocardiographic findings identified during the study) will be communicated directly to participants and their treating physicians at the time of assessment, consistent with standard clinical care.

Research findings will also be available at www.ClinicalTrials.gov, the Sri Lankan Clinical Trials Registry, and published in the form of research articles or presented at scientific meetings.

21. DATA SHARING AND DISSEMINATION

The trial will be registered prospectively on ClinicalTrials.gov and the Sri Lanka Clinical Trials Registry. Summary results will be reported on both registries within 12 months of primary study completion. De-identified participant-level data and accompanying data dictionaries will be made available to qualified investigators upon reasonable request and following approval by the Steering Committee, consistent with NIH data-sharing policies. Requests must include a methodologically sound proposal and a data use agreement ensuring participant confidentiality.

Primary and secondary study findings will be disseminated through:

- Peer-reviewed scientific publications
- Presentations at national and international conferences
- Stakeholder briefings with Sri Lankan clinicians and health system leaders

22. STUDY TIMELINE

The total study duration is expected to be approximately 42 months**,** including start-up, recruitment, follow-up, data analysis, and dissemination.

Key Milestones

Study Phase	Timeline
Regulatory approvals (IRB, NMRA, ERC)	Months 0–6
Site initiation and staff training	Months 4–6
Participant recruitment and enrollment	Months 6–24
Minimum participant follow-up	Months 6–36
Extended follow-up to common study end date	Months 18–36
Database lock and final analyses	Months 36–39
DSMB final review	Months 38–40
Manuscript preparation and dissemination	Months 39–42
Results reporting to registries	Within 12 months of study completion

Participants will be followed for a minimum of 12 months, with additional follow-up until the common study end date to ensure complete ascertainment of the primary outcome.

23. PROTOCOL SIGNATURE PAGE

The signatures below constitute approval of this protocol by the signatories and provide the assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, applicable by ethical and regulatory requirements, laws and ICH-GCP.

The investigators affirm that any financial relationships, commercial interests, or potential conflicts of interest related to the study have been fully disclosed in accordance with institutional and regulatory requirements. Any intellectual property arrangements relevant to the study will be transparently managed and reported in accordance with applicable institutional policies.

The investigators further confirm that the design, conduct, analysis, interpretation, and reporting of the study will be carried out independently by the investigators, ensuring full scientific integrity and transparency regardless of funding sources or other forms of support.

PROTOCOL ID NUMBER: _____

Principal Investigator
Signature:

Date: 22 May 2026

Name: Anubha Agarwal, MD MSc

Title: Assistant Professor of Medicine, Co-Director Program in Global Cardiovascular Health
Division of Cardiology, Department of Medicine Washington University in St. Louis

Trial Site Investigator

Trial Site Name: _____

Signature: _____

Date: _____

Name: _____

Title: _____

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