Developing a Heart Failure Polypill to Reduce Total Pill Burden Among People Living with HIV: A Pilot Crossover Randomized Controlled Trial (COMBO HF-X): Statistical Analysis Plan

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1. Study Rationale/Background

Heart failure with reduced ejection fraction (HFrEF) has a five-year mortality of approximately 50%. A four-drug regimen for HFrEF is highly effective, but is associated with high daily pill burden. A four-drug regimen for HFrEF, referred to as guideline-directed medical therapy (GDMT), is associated with a 73% relative reduction in mortality at 2 years in addition to preventing hospital admissions and improving quality of life.[1] Despite these benefits, the associated pill burden—ranging from 4-8 tablets per day—is a significant barrier to adherence, with an estimated 40-60% of patients with HFrEF missing a significant number of doses.[2] In turn, non-adherence is associated with hospital readmissions and increased mortality. Despite compelling evidence that pill burden negatively impacts adherence, there is no combination pill for HFrEF available in the US. In this pilot feasibility trial, we evaluated whether an over-encapsulated polypill—prepared at the pharmacy to contain patients' customized GDMT—would improve adherence and would be feasible and acceptable to patients. We recruited a subgroup of patients with HIV, who experience higher rates of HFrEF than the general population and, despite the availability of single-pill combination ART, are facing higher daily pill burden due to cardiovascular and other comorbidities.[3]

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2. Mastromarino V, Casenghi M, Testa M, et al. Polypharmacy in Heart Failure Patients. *Curr Heart Fail Rep*. 2014;11(2):212-219. doi:10.1007/s11897-014-0186-8

3. Krentz HB, Gill MJ. The Impact of Non-Antiretroviral Polypharmacy on the Continuity of Antiretroviral Therapy (ART) Among HIV Patients. *AIDS Patient Care and STDs*. 2016;30(1):11-17. doi:10.1089/apc.2015.0199

2. Study Objectives

a. Overview

COMBO-HF-X is a randomized, open-label, single-center crossover proof-of-concept/pilot clinical trial designed to test the preliminary adherence effects, feasibility and acceptability of customized over-encapsulated HFrEF polypills as a strategy to improve delivery of GDMT in a safety-net healthcare system.

b. Primary Hypothesis and Objective

a. Objective: To determine the effect of a polypill intervention on adherence to HF GDMT compared to usual care with individual tablets.
b. Primary Hypothesis: Compared with usual care, co-packaging of heart failure therapies into an over-encapsulated polypill will increase adherence to GDMT at 4 weeks and reduce total daily pill burden among patients with HFrEF.

c. Secondary Objective 1 and Hypothesis

a. Objective: Determine feasibility of recruitment and retention for a polypill clinical trial for people with low reported baseline adherence within a safety-net setting.
b. Primary Hypothesis: Recruiting 30-40 participants within 12 months and retaining at least 20 through study completion will be feasible.

d. Secondary Objective 2 and Hypothesis

a. Objective: Determine acceptability of the polypill intervention.
b. Primary Hypothesis: Participants will prefer the polypill intervention over individual tablets and will find the polypill intervention acceptable.

e. Exploratory Objectives

a. Objective: Determine impact of the polypill intervention on additional clinical parameters.
b. Primary Hypothesis: The polypill intervention may be associated with improvements in clinical parameters such as blood pressure and KCCQ-12 score.
c. Objective: Determine preliminary cost and time estimates for pharmacy partner to prepare polypills.
d. Primary Hypothesis: N/A (we will measure time and cost).
e. Objective: Determine participant perspectives on acceptability, barriers and facilitators to polypills via surveys and semi-structured exit interviews.
f. Primary Hypothesis: The polypill intervention will be viewed as acceptable by patients.

3. Study Population

Adults with HFrEF (last LVEF <50%). We will target a sample size of 30–40 participants but will adjust the sample size based on logistical constraints that may emerge during the pilot study. Participants will be recruited primarily using a heart failure registry in the electronic medical record. As described above, we will recruit a subgroup of patients with HFrEF and HIV.

a. Inclusion criteria

- Adults aged 18 or older with a diagnosis of heart failure and ejection fraction<50% on their most recent echocardiogram or cardiac MRI.
- Last estimated glomerular filtration rate (eGFR) >30 mL/min/1.73 m^2.
- Able to conveniently obtain medications through one of three available mechanisms (mail, pick up at a Zuckerberg San Francisco General Hospital clinic, or pick up at the partner pharmacy).
- Working phone number for telephone visits.

b. Exclusion criteria

- Patients who are already prescribed all recommended pillars of guideline-directed medical therapy (GDMT) and report 100% adherence to GDMT.

- Patients who are not fluent in English.
- Patients who are incarcerated.
- Patients who cannot provide informed consent.
- Patients with a ventricular assist device or patients with a myocardial infarction, unstable angina, stroke or transient ischemic attack within 12 weeks prior to enrolment.
- Women who are pregnant, breastfeeding or might become pregnant during the study period and are not planning to use medically acceptable forms of contraception (pharmacological or barrier methods).
- Concomitant medical condition which in the opinion of the study team could interfere with the safe conduct of the study including outcome assessment.
- 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.
- Participant's responsible physician believes it is not appropriate for participant to take part in the study.
- Unable to complete study procedures and/or plan to move out of the study area in the next 2 months.

c. Power and Sample Size Considerations

As a pilot study, the primary goal is to inform future trials and point estimates of adherence will have limited generalizability and should be interpreted with caution. Considering a power of 80% and a two-sided alpha of 5%, using a two-treatment crossover trial design, we estimate that a minimum sample size of 20 participants (10 per arm) will be necessary to identify a 20% absolute change in adherence ratio between the HFrEF polypill and usual care conditions, assuming an SD of 30% in repeated measurements of an individual's adherence ratio over time. Assuming up to a 50% dropout rate in this safety-net healthcare setting, we estimate that 30–40 patients should be recruited.

4. Statistical Analysis Plan

Table 4.1: Analysis Variable Definitions

Analysis	Variables	Variable Type	Time points
Outcome			
Primary: Adherence	Adherence to guideline-directed medical therapy	Continuous	4 weeks and 8 weeks

	(GDMT) overall, as measured by pill count Adherence to GDMT overall will be calculated as the mean adherence proportion (number of pills missing/number of pills that should have been missing) for each individual class of GDMT		
Feasibility of Recruitment	Recruitment of 30–40 participants within 1 year of initiating recruitment	Binary	After Completing Enrollment
Feasibility of adherence to study protocols	Completion of study procedures for at least 20 participants (screening, randomization, follow-up procedures, retention and transition to ongoing care)	Binary	After Completing Study Activities
Time to prepare 1 month s supply of polypill at our community pharmacy partner	Minutes per participant	Continuous	At beginning of polypill intervention period
Cost to prepare 1 month supply of polypill at our community pharmacy partner	Cost per participant	Continuous	At beginning of polypill intervention period
Morisky Medication Adherence-8 (MMAS-8) Questionnaire	Total Score	Continuous	0, 4 and 8 weeks
Treatment Satisfaction for Medication Questionnaire	Global Satisfaction Score, Convenience Score, Effectiveness Score	Continuous	0, 4 and 8 weeks
Number of GDMT pillars prescribed	Beta-blocker, ACE/ARB/ARNI, MRA, SGLT2i	Categorical	0, 4 and 8 weeks
Heart failure admission		Binary	0, 4 and 8 weeks
Kansas City Cardiomyopathy Questionnaire (KCCQ) 12 Score	KCCQ-12 Overall Summary Score, KCCQ-12 Clinical Summary Score	Continuous	0, 4 and 8 weeks

Adherence to each individual component of GDMT by pill count	Calculated adherence for each of the 4 pillars using adherence ratio (consistent with primary outcome)	Continuous	0, 4 and 8 weeks
Blood pressure (mm Hg)	Systolic, diastolic	Continuous	0, 4 and 8 weeks
Heart rate (beats per minute)	Heart rate	Continuous	0, 4 and 8 weeks
Weight	Weight		0, 4 and 8 weeks
NT-proBNP	NT-proBNP		0, 4 and 8 weeks
Total daily pill burden	Total pill count estimated based on the EMR list of active outpatient prescriptions	Continuous	0, 4 and 8 weeks
HFrEF polypill patient satisfaction exit survey	Preference for Polypill, Ease of Use, Worry about Safety, Desire to Continue Polypill, Higher HF Adherence, Higher non-HF Adherence, Feeling Better about Meds, Feeling Better Physically, AIM measure	Survey Questionnaire (including Likert-type questions)	8 weeks
Qualitative Interview	Semi-structured interview	Qualitative	8 weeks
Serious Adverse Events	Serious Adverse Event (mortality, heart failure admission, non-heart failure admission)	Count of events and count of participants with each event	0, 2, 4, 6, 8 weeks through participant contact and medical records; retrospectively using medical records for up to 30 days after completion of the study
Non-Serious Adverse Events of Special Interest	HF ER or urgent care visit not resulting in hospitalization, non-HF ER or urgent care visit not resulting in hospitalization, Acute kidney injury, Hyperkalemia, Dizziness or hypotension, Medication discontinuation or down-titration due to intolerance	Count of events and count of participants with each event	0, 2, 4, 6, 8 weeks through participant contact and medical records; retrospectively using medical records for up

			to 30 days after completion of the study
Primary Exposure(s)			
Assignment to Polypill first versus Individual Tablets first			
Other Covariates			
Age		Continuous	Baseline
Sex Assigned at Birth		Binary	Baseline
Gender		Categorical	Baseline
Race		Categorical	Baseline
Hispanic/Latino/Latina Ethnicity		Binary	Baseline
Left Ventricular Ejection Fraction		Continuous	Baseline
RV dysfunction on echocardiogram		Binary	Baseline
Time since last outpatient cardiology visit		Continuous	Baseline
Heart Failure Hospitalization within past 3 months		Binary	Baseline
Comorbidities	HIV, Hypertension, Hyperlipidemia, Diabetes, Atrial fibrillation or flutter, Chronic Kidney Disease, Coronary Artery Disease, Chronic Obstructive Pulmonary Disease, Depression or Anxiety	Binary	Baseline
Drug Use	Stimulant Use (current/former), alcohol use (current/former), Tobacco (current/former)	Categorical	Baseline

a. Primary Analysis:

a. Analysis overview

Analyses will follow the intention-to-treat principle including all randomized participants to the extent possible. Per protocol analyses will be conducted as well as sensitivity analyses.

First we will compare baseline characteristics of the group randomized to polypill first with the group assigned individual tablets first. We will use the Wilcoxon rank-sum test for continuous variables that are not normally

distributed and Student's t test for continuous variables that are normally distributed. We will use Fisher's exact test or Pearson's chi-squared test for categorical variables depending on the number of counts in each cell. Participants with missing data will be omitted.

For the primary analysis, we will compare overall adherence ratio to GDMT between treatment conditions using mixed-effects models. Given that this is a crossover analysis, we will first test for a period effect using mixed-effects models that include fixed effects for period and treatment and random effects for participant. If there is no significant period effect at the $p<0.05$ level, we will then evaluate treatment effect using mixed-effects models that include fixed effects for treatment, order, and treatment-order interaction and random effects for participant. Assuming that the primary outcome is missing completely at random, the primary analysis will use a complete case approach, that is, will only include participants who completed both arms of the study and have pill count data for each prescribed class of GDMT. Participants with partial pill count data will be included in a secondary analysis; if there is evidence to support that pill counts are not missing at random then we will consider alternative approaches including using partial or estimated pill counts. For the primary outcome, the threshold for statistical significance will be a two-sided $p<0.05$ without adjustment for multiple testing. We will estimate the mean and 95% confidence interval of the mean for each outcome in the polypill state and individual tablet state.

For all safety endpoints, we will include those who were randomized and received at least one dose of at least one intervention period (ie excluding those who drop out prior to beginning the intervention). We will report the number of events overall and the number of participants who experience each event. We will compare events by group using the Fisher's exact test.

We will report whether two feasibility endpoints were met: (1) recruitment of 30–40 participants within a 1-year study period and (2) successful completion of study procedures for at least 20 participants. For the participant exit survey, responses to Likert-style questions (ranging from 1 (completely disagree) to 5 (completely agree) will be reported with means and SD for each measure. For implementation outcomes, we will report the preparation cost and mean time spent by the pharmacy to prepare a 1-month supply of HFrEF polypills.

For qualitative data, we will use rapid qualitative analysis (RQA) methods, employing the Planning for and Assessing Rigor in Rapid Qualitative Analysis framework to develop data analysis templates and summarize key themes from interviews with patients, prescribers and pharmacy staff.

b. Figures/Tables
Table 1: baseline clinical characteristics by treatment assignment (polypill first vs individual tablets first)

Table 2: primary, secondary, and exploratory endpoints by group (polypill vs individual tablets).
Figure 1: CONSORT Diagram
Figure 2: Mean adherence Polypill vs Individual Tablets
Figure 3: Waterfall plot

c. Sensitivity analyses
    i. Inclusion of partial pill counts
    ii. Capping adherence at 100%
d. Subgroup/Exploratory analyses
    i. We will conduct exploratory secondary analyses in which we stratify the sample according to (1) baseline adherence according to MMAS-8 score, (2) HIV status, (3) total daily pill burden at baseline, (4) baseline stimulant use.

b. Secondary Analysis:

a. Analysis overview
Analysis of other continuous secondary outcomes will follow the same analytic plan as the primary outcome; for these outcomes we will include all randomized participants with data for that outcome at 4 and 8 weeks.