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

University of California Institutional Review Board
Study #23-39360 Protocol Version 1.6
Approved September 11, 2023

ClinicalTrials.gov identifier: NCT06029712

Principal Investigators
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Priscilla Hsue, MD

Funding
UCSF CAPS-HIV Innovative Grant (P30MH062249), UCSF Center for AIDS Research, UCSF CFAR/ARI HIV Boost Award, and the National Center for Advancing Translational Sciences, National Institutes of Health, through UCSF-CTSI Grant Number UL1 TR001872.

Study Application (Version 1.6)

1.0 General Information

***Enter the full title of your study:**

Developing a Heart Failure Polypill to Reduce Total Pill Burden: A Pilot Crossover Randomized Controlled Trial

***Enter the study alias:**

Pilot Trial
* This field allows you to enter an abbreviated version of the Study Title to quickly identify this study.

2.0 Add departments

2.1 and Specify Research Location:

Is Primary?	Department Name
◉	**UCSF** - *138310* - M_MED-CORE-CARD

3.0 List the key study personnel: (Note: external and affiliated collaborators who are not in the UCSF directory can be identified later in the Qualifications of Key Study Personnel section at the end of the form)

3.1 *Please add a Principal Investigator for the study:

Dejong, Colette C

Select if applicable

☐ Department Chair ☐ Resident

☑ Fellow

If the Principal Investigator is a Fellow, the name of the Faculty Advisor must be supplied below.

3.2 If applicable, please select the Research Staff personnel

A) Additional Investigators

Davis, Jonathan
Other Investigator
Durstenfeld, Matthew S MD
Other Investigator
Hickey, Matthew D MD, MD
Other Investigator
Hsue, Priscilla MD, MD
Co-Principal Investigator
Riley, Elise PhD

Other Investigator
Steward, Wayne PhD
Other Investigator
Zier, Lucas S
Other Investigator

B) Research Support Staff

Levkova, Marta
Study Coordinator
Li, Danny
Clinical Research Associate
Schaffer, Veronica
Study Coordinator

3.3 *Please add a Study Contact

Dejong, Colette C

The Study Contact(s) will receive all important system notifications along with the Principal Investigator. (e.g. The project contact(s) are typically either the Study Coordinator or the Principal Investigator themselves).

3.4 If applicable, please add a Faculty Advisor/Mentor:

Hsue, Priscilla MD, MD

3.5 If applicable, please select the Designated Department Approval(s)

Hsue, Priscilla MD, MD
Department Chair

Add the name of the individual authorized to approve and sign off on this protocol from your Department (e.g. the Department Chair or Dean).

4.0 Initial Screening Questions

Updated Sept 2022 - Revised Common Rule (January 2018) Compliant / COVID-19 - v98

4.1 * PROJECT SUMMARY: (REQUIRED) Give a brief overview of this project (250 words or less). Tell us what this study is about, who is being studied, and what it aims to achieve. If you have an NIH Abstract, paste it here (Click on the orange question mark to the right for more detailed instructions):

A novel four-drug regimen for heart failure with reduced ejection fraction (HFrEF) extends patients' life expectancy by an average of 6 years compared to traditional therapies, in addition to improving quality of life. Unfortunately, uptake of this complex multi-drug regimen has been low, especially among underserved communities with barriers to medication adherence. Although combination tablets have transformed access to care for conditions such as HIV and tuberculosis, no combination pill is available for HFrEF.

In the proposed study, we will partner with a pharmacy to package several heart failure medications into a single capsule ("polypill") for patients living with HIV and HFrEF, with the goal of reducing total daily pill burden and improving adherence among PWH impacted by

polypharmacy. In **Aim 1,** we will first conduct stakeholder interviews with patients, providers, and pharmacists to inform the design of a HFrEF polypill (separate IRB # 22-38189). In **Aim 2 (present IRB application)**, we will conduct a pilot, single-center, crossover randomized clinical trial to investigate whether, compared to usual care, a HFrEF polypill increases medication adherence among 40 adults with HFrEF. This pilot work will be funded by a grant from the UCSF CAPS-HIV Innovative Grant. Based on these findings, our group intends to submit a PCORI grant application to fund a larger RCT of cardiovascular polypills among people with HIV.

4.2 * HUD DEVICE: (REQUIRED) Does this application involve a Humanitarian Use Device (HUD):

- (•) No
- ( ) Yes, and it includes a research component
- ( ) Yes, and it involves clinical care ONLY

4.3 * TYPE OF RESEARCH: (REQUIRED) Select the option that best fits your project (Click the orange question mark to the right for definitions and guidance):

- (•) Biomedical research (including medical records review, biospecimen collection and/or use, other healthcare or health outcomes related activities, research database, biospecimen bank, or recruitment registry)
- ( ) Social, behavioral, educational, and/or public policy research
- ( ) Hybrid - includes aspects of BOTH types of research (check this option if your research is mainly social/behavioral but also involves specimen collection or blood draws to look at biological measures)

4.4 * SUBJECT CONTACT: (REQUIRED) Does this study involve ANY contact or interactions with participants:

- (•) Yes (including phone, email or web contact)
- ( ) No (limited to medical records review, biological specimen analysis, and/or data analysis)

4.5 * RISK LEVEL: (REQUIRED) What is your estimation of the risk level, including all screening procedures and study activities:

- (•) Minimal risk
- ( ) Greater than minimal risk

4.6 * REVIEW LEVEL: (REQUIRED) Requested review level (Click on the orange question mark to the right for definitions and guidance):

- (•) Full Committee
- ( ) Expedited
- ( ) Exempt

Generally, only *Greater than Minimal Risk* studies require *Full Committee Review*. We suggest you check *Expedited Review* instead or change the risk level, if you checked the wrong box.

4.9 * DATA/SPECIMEN ANALYSIS ONLY: (REQUIRED) Does this study ONLY involve records review and /or biospecimen analysis (do not check 'Yes' if this is a registry, research or recruitment database, or biospecimen repository):

- ( ) Yes (•) No

4.10 * CLINICAL TRIAL: (REQUIRED)

Is this a clinical trial:

According to The World Health Organization (WHO) and the International Committee of Medical Journal Editors (ICMJE) a clinical trial is:

- Any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes.

ICMJE requires registration of a clinical trial in a public database (such as ClinicalTrials.gov) prior to enrollment, for eventual publication of results in member biomedical journals.
Guidance: Public Law 110-85 requires that all investigators who perform an *applicable clinical trial* must ensure that the trial is registered on a government web site called **ClinicalTrials.gov**.

The FDA requires registration for 'applicable clinical trials,' defined as follows:

- For any trials of drugs and biologics: controlled clinical investigations, other than Phase 1 investigations, of a product subject to FDA regulation.
- For trials of biomedical devices: controlled trials with health outcomes of devices subject to FDA regulation, other than small feasibility studies, and pediatric post-market surveillance.

For additional information on the **ClinicalTrials.gov** registration process at UCSF and the definition of a clinical trial for purposes of registration, visit the **ClinicalTrials.gov section of the UCSF Clinical Research Resource HUB**.

(•) Yes ( ) No

Clinical Trial Registration - 'NCT' number for this trial:

NCT06029712

4.11 * CLINICAL TRIAL PHASE: (REQUIRED) Check the applicable phase(s):

- [ ] Phase 0
- [ ] Phase 1
- [ ] Phase 1/2
- [x] Phase 2
- [ ] Phase 2/3
- [ ] Phase 3
- [ ] Phase 4
- [ ] Not Applicable

4.12 * INVESTIGATOR-INITIATED: (REQUIRED) Is this an investigator-initiated study:

(•) Yes ( ) No

The UCSF IRB recommends use of the Virtual Regulatory Binder to manage your study.

4.13 * CORONAVIRUS RESEARCH: (REQUIRED) Does this study involve research on coronaviruses (COVID-19, SARS, MERS or other):

- ○ Yes
- ◉ No

4.15 * CANCER: (REQUIRED) Does this study involve cancer (e.g., the study involves patients with cancer or at risk for cancer, including behavioral research, epidemiological research, public policy research, specimen analysis, and chart reviews):

- ○ Yes
- ◉ No

4.16 * RADIATION EXPOSURE: (REQUIRED) Does your protocol involve any radiation exposure to patients /subjects EITHER from standard care OR for research purposes (e.g., x-rays, CT-scans, DEXA, CT-guided biopsy, radiation therapy, or nuclear medicine including PET, MUGA or bone scans):

- ○ Yes
- ◉ No

4.17 * HIV SCREENING: (REQUIRED)Does this study involve screening for HIV infection:

You should answer 'Yes' if the protocol includes HIV testing even if it's just for screening to determine eligibility.

- ○ Yes
- ◉ No

4.18 * SCIENTIFIC REVIEW: (REQUIRED) If this study has undergone scientific or scholarly review, please indicate which entity performed the review (check all that apply):

- ☑ Funding agency, cooperative group, study section or other peer-review process
- ☐ Cancer Center Protocol Review Committee (PRC) (Full approval is required prior to final IRB approval for cancer-related protocols.)
- ☐ CTSI Clinical Research Services (CRS) Advisory Committee
- ☐ Departmental scientific review
- ☐ CTSI Consultation Services
- ☐ Other:
- ☐ Has not undergone scientific/peer review

* Specify entity that provided review: **(REQUIRED)**

UCSF CAPS-HIV Innovative Grant (funded project)

4.19 * STEM CELLS: (REQUIRED)Does this study involve human stem cells (including iPS cells and adult stem cells), gametes or embryos:

- ◉ No
- ○ Yes, and requires IRB and GESCR review
- ○ Yes, and requires GESCR review, but NOT IRB review

4.20 * FINANCIAL INTERESTS: (REQUIRED) Do you or any other responsible personnel (or the spouse, registered domestic partner and/or dependent children thereof) have financial interests related to this study:

○ Yes ◉ No

5.0 Funding

5.1 * FEDERAL FUNDING: (REQUIRED) Is this study currently supported in whole or in part by Federal funding, *even by a subcontract*, OR has it received ANY Federal funding in the past:

○ Yes ◉ No

5.2 * DoD INVOLVEMENT: Is this project linked in any way to the Department of Defense (DoD): (REQUIRED)

○ Yes ◉ No

5.3 SPONSORS:

External Sponsors: Identify all sponsors, funding sources, and entities that are contributing to the conduct of this study in a material way:

- **If funding comes from a Subcontract, please list only the Prime Sponsor (i.e. list "Bayer" instead of "Stanford University.")**
- **For drug and device donation agreements, select "Drug/Device Donation" under "Contract Type."**

For all studies with funding through UCSF, *either* the Award Number (A Number) *OR* the Proposal Number (P Number) is required (not both, even though they both display a red asterisk).

- **The A Number is preferred but may not be available when a new study is first submitted.**
- **The P Number is created by the UCSF Office of Clinical Trial Activation (OCTA) when they receive the study. If you don't have a P Number yet because the study has not yet been submitted to OCTA, send an email to clinicaltrials@ucsf.edu.**
- **If funds are awarded before IRB approval is obtained, please provide the A Number.**
- **If the submission is approved before the A Number is available, please provide the A Number the next time you submit changes to the Study Application but do not submit a Modification only to add the A Number.**

View Details	Sponsor Name	Sponsor Type	Awardee Institution:	Contract Type:	Project Number	UCSF RAS System Award Number ("A" + 6 digits)
	American College of		Other (No funding comes			

⊟	Cardiology, Inc.	05	through UCSF C&G unit)			

Sponsor Name:	American College of Cardiology, Inc.
Sponsor Type:	05
Sponsor Role:	Funding
CFDA Number:	
Grant/Contract Number:	
Awardee Institution::	Other (No funding comes through UCSF C&G unit)
Is Institution the Primary Grant Holder:	No
if No, then who is the Primary Grantee?	Colette DeJong
Contract Type:	
Project Number:	
UCSF RAS System Award Number ("A" + 6 digits):	
Grant Number for Studies Not Funded thru UCSF:	
Grant Title:	ACC/ABC Merck Research Fellowship Award (salary support for Colette DeJong)
PI Name: (If PI is not the same as identified on the study.)	
Explain Any Significant Discrepancy:	

Other Funding Sources and Unfunded Research - Gift, Program, Departmental or other Internal Funding (check all that apply):

- ☐ Funded by gift (specify source below)
- ☑ Funded by UCSF or UC-wide program (specify source below)
- ☐ Specific departmental funding (specify source below)
- ☐ Unfunded (miscellaneous departmental funding)
- ☐ Unfunded student project

* Identify the gift, program, departmental, or other internal funding source: **(REQUIRED)**

CAPS-HIV Innovative Grant, CFAR-ARI HIV Research Boost Award

6.0 Sites, Programs, Resources, and External IRB Review

6.1 * UCSF AND AFFILIATED SITES (check all that apply): (REQUIRED)

- ☐ UCSF Benioff Children's Hospital Oakland (BCH OAK)
- ☐ UCSF Cancer Center Berkeley
- ☐ UCSF Cancer Center San Mateo
- ☐ UCSF China Basin clinics and facilities
- ☐ UCSF Helen Diller Family Comprehensive Cancer Center
- ☐ UCSF Langley Porter Psychiatric Institute (LPPI)
- ☐ UCSF Medical Center at Mission Bay (Benioff Children's Hospital, the Betty Irene Moore Women's Hospital, Bakar Cancer Hospital, or outpatient clinics)

- [ ] UCSF Mount Zion
- [ ] UCSF Parnassus (Moffitt-Long hospital, dental clinics or other outpatient clinics)
- [ ] UCSF Other Sites (including Laurel Heights and all the other sites outside the main hospitals and clinics)
- [ ] UCSF Fresno
- [ ] Gladstone Institutes
- [ ] Institute on Aging (IOA)
- [ ] Jewish Home
- [ ] SF Dept of Public Health (DPH)
- [ ] San Francisco VA Health Care System (SFVAHCS) – including Community-Based Outpatient Clinics (CBOCs)
- [ ] Vitalant (formerly Blood Centers of the Pacific and Blood Systems Research Institute)
- [x] Zuckerberg San Francisco General (ZSFG)

Research involving SFDPH/ZSFG: A UCSF Research at SFDPH Protocol Application is required for all research. Review this link for more information and contact information for SFDPH/ZSFG questions. SFDPH sites and clinics have special requirements that you must be familiar with. The UCSF IRB will only review SFDPH IRB Applications with designated SFDPH PIs.

6.2 * LOCATIONS: At what locations will study visits and activities occur: (REQUIRED)

Zuckerberg San Francisco General Hospital – inpatient service, cardiology clinics, and Ward 86 Positive Health Program

6.3 OFF-SITE PROCEDURES: Will any study procedures or tests be conducted off-site by non-UCSF personnel:

- ○ Yes
- ◉ No

6.4 RESEARCH PROGRAMS: Check any UCSF research programs this study is associated with:

- [ ] Cancer Center
- [x] Center for AIDS Prevention Sciences (CAPS)
- [ ] Global Health Sciences
- [ ] Immune Tolerance Network (ITN)
- [ ] Neurosciences Clinical Research Unit (NCRU)
- [ ] Osher Center
- [x] Positive Health Program
- [ ] Weill Institute for Neurosciences Translational Research Unit (WIN TRU)

6.5 * CTSI CRS SERVICES: (REQUIRED)Will this study be carried out at one of the UCSF Clinical Research Services (CRS) Units or utilize CRS Service:

- ◉ Yes
- ○ No

6.6 * MULTI-CENTER TRIAL: (REQUIRED) Is this a multi-center or multi-site research trial:

By '**multi-center trial**' we mean a study where the protocol is developed by an lead investigator, an industry sponsor, consortium, a disease-group, etc.,and multiple sites across the nation or in different countries participate in the trial. The local sites do not have any control over the design of the protocol.

○ Yes ◉ No

6.8 OTHER SITE TYPES: Check all the other types of sites not affiliated with UCSF with which you are cooperating or collaborating on this project:

Do NOT check any boxes below if this is a multi-center clinical trial, UCSF is just one of the sites, and neither UCSF nor one of its faculty-linked affiliates (SF VAHCS, Gladstone, ZSFG) are the coordinating center.

- ☐ Other UC Campus
- ☑ Other institution
- ☑ Other community-based site
- ☐ Foreign Country
- ☐ Sovereign Native American nation (e.g. Navajo Nation, Oglala Sioux Tribe, Havasupai, etc.)

6.11 * OUTSIDE RELIANCES: (REQUIRED) Are any of the collaborating sites requesting to rely on UCSF's IRB:

○ Yes ◉ No

6.15 * RELYING ON AN EXTERNAL IRB: (REQUIRED) Does this application include a request to rely on an external IRB (a central IRB (other than the NCI CIRB) or an external IRB (other UC campus, commercial, or institutional):

○ Yes ◉ No

7.0 Outside Site Information

7.1 Outside Site Information

If you have more than 10 sites to add, list the outside sites in the Outside Sites List document and upload it in the Other Study Documents section of the Initial Review Submission Packet form. Any sites requesting to rely on UCSF's IRB must be listed below.

Click "Add a new row" to enter information for a site. Click it again to add a second site again to add a third site, a fourth site, etc.

Outside Site Information

Non-UCSF affiliated site information:

Site name:

Washington University in St. Louis

Contact name:

Justin Chen

Email:

justin.chen@wustl.edu

Phone:

314-792-0201

For Federally-funded studies only, corresponding FWA#:

*** The research at this site will be reviewed by:**

- ○ The non-affiliated site's IRB or a private IRB
- ○ The non-affiliated site is requesting UCSF to be the IRB of record for this study
- ◉ The non-affiliated site is not engaged in the human subjects research and has provided a letter of support

If the other site's IRB approval letter is available now, attach it to the application. If the IRB approval letter is not yet available, submit it once you receive it.

Or, if the other site is **not engaged** in human subjects research, attach the letter of support to your application.

Outside Site Information

Non-UCSF affiliated site information:

Site name:

Daniel's Pharmacy

Contact name:

Iyad I. Nasrah, RPh

Email:

inasrah@gmail.com

Phone:

(415) 584-2210

For Federally-funded studies only, corresponding FWA#:

*** The research at this site will be reviewed by:**

- ○ The non-affiliated site's IRB or a private IRB
- ○ The non-affiliated site is requesting UCSF to be the IRB of record for this study
- ◉ The non-affiliated site is not engaged in the human subjects research and has provided a letter of support

If the other site's IRB approval letter is available now, attach it to the application. If the IRB approval letter is not yet available, submit it once you receive it.

Or, if the other site is **not engaged** in human subjects research, attach the letter of support to your application.

8.0 Research Plan and Procedures

8.1 * HYPOTHESIS: Describe the hypothesis or what the study hopes to prove: (REQUIRED)

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 HIV and HFrEF.

8.2 * AIMS: List the specific aims: (REQUIRED)

In the proposed study, we will utilize inexpensive over-encapsulation techniques to develop a HFrEF combination pill ("polypill") for patients living with HFrEF, with and without HIV, with the goal of reducing total daily pill burden and improving adherence among PWH impacted by polypharmacy.

To accomplish this, we will develop a clinical workflow through which participants' HFrEF medications are over-encapsulated into a single, individualized polypill capsule at the pharmacy. Like a bubble pack, in which pharmacists sort a patient's morning and evening doses into pre-filled compartments to facilitate adherence, the polypill will be individualized to each patient and will not interfere with medication dosing or titration (Supplemental Figure). Thus, the proposed study is a medication packaging intervention, similar to a bubble pack. In a small pilot study, we will evaluate whether a HFrEF polypill improves adherence among adult patients with HFrEF at Zuckerberg San Francisco General Hospital (ZSFG).

In **Aim 1,** we will conduct formative interviews of patients, pharmacists, HIV primary care clinicians, infection disease specialists, and cardiologists to characterize barriers to ART and GDMT adherence and elicit perspectives on a HFrEF polypill. This qualitative aim is covered by a separate CHR application (IRB # 22-38189).

In **Aim 2**, we will conduct a pilot, single-center, crossover randomized clinical trial to investigate whether, compared to usual care, a HFrEF polypill implementation strategy increases adherence to GDMT with no increase in serious adverse events among adults with HFrEF. We aim to recruit an HIV+ subgroup (~10-20 participants) and an HIV- subgroup (~10-20 participants). The estimated sample size will be 20-40, but we will plan from the onset to modify the total sample size in response to logistical constraints during this pilot study. Key secondary outcomes will include total daily pill burden, adherence to ART, and the Treatment Satisfaction Questionnaire for Medication, as well as feasibility measures around the polypill (cost, production time). This pilot study will not be powered for clinical outcomes, but exploratory outcomes will include heart failure admissions and the Kansas City Cardiomyopathy Questionnaire.

8.3 * DESIGN: Briefly describe the study design (e.g., observational, interventional, randomized, placebo-controlled, blinded, cross-over, cross-sectional, longitudinal, pharmacokinetic, etc.): (REQUIRED)

Pilot phase II open-label randomized controlled trial with a 2x2 crossover design (AB/BA). The trial will examine whether over-encapsulation of several heart failure therapies into a single capsule is feasible and improves adherence and treatment satisfaction. Like a bubble pack or

Medi-Set, the intervention is a delivery strategy for well-established, guideline-directed therapies for heart failure.

8.4 * BACKGROUND AND SIGNIFICANCE: Briefly provide the background and significance of this study (e. g. why is this study needed) (space limit: one half page): (REQUIRED)

If this is a first in humans study, please summarize the safety data from the animal studies. For pediatric drug or device studies, please identify if this is the first study in pediatric populations.

Reduction of total daily pill burden among PWH is associated with improved ART adherence and viral suppression, and has become a priority within HIV prevention and treatment. In an era of highly-effective treatments for HIV, medication acceptability and adherence have become key public health challenges. Pill burden has been identified as one of the most easily modifiable drivers of adherence to ART. The adverse effects of pill burden are amplified among patients with additional barriers to adherence, such as housing instability or stimulant use disorder. In a longitudinal study of people living with HIV who use drugs by Alvi et al, each additional pill was negatively associated with medication adherence (adjusted odds ratio of 0.87 per pill, 95% confidence interval 0.84-0.91).[1]Single-tablet ART regimens have become first line, and long-acting injectable therapies have made viral suppression accessible to more patients.

Pill burden among PWH declined with single-tablet ART, but has started to rise again due to comorbidities in an aging population.[2] Over half of PWH in the U.S. are over 50, and non-ART medications now comprise the majority of daily pill burden for many PWH. In focus groups of patients and providers at ZSFG's Golden Compass Clinic, management of comorbidities was a commonly cited issue, and interventions to support ART adherence were a shared priority of both patients and providers.[3] Total daily pill burden is rising faster among PWH than the general population, driven primarily by polypharmacy for cardiovascular and other comorbidities. PWH are at a two-fold increased risk of cardiovascular disease (CVD), which now accounts for 1 in 5 deaths among PWH in the U.S. Polypharmacy can dilute the impact of single-tablet ART on total daily pill burden, leaving PWH at risk for pill fatigue and associated non-adherence.[2]

Heart failure with reduced ejection fraction (HFrEF) is one of the most serious cardiovascular comorbidities among PWH, with a five-year mortality of approximately 50%. A four-drug regimen for HFrEF is highly effective, but significantly increases total daily pill burden among PWH. People with HIV are more likely to be diagnosed with HFrEF and more likely to die from heart failure, with the highest risk among patients with a detectable HIV viral load and patients who also use stimulants.[4] In a cohort study of 2,308 patients admitted to an academic medical center in the Bronx with decompensated HFrEF, patients with HIV were at increased risk of cardiovascular mortality (28% vs. 15%) and all-cause mortality (41% vs. 26%) compared to non-infected individuals.[4] Patients with a detectable HIV viral load were at even higher risk of cardiovascular death (47%) and all-cause mortality (65%), and had a 70% risk of 30-day readmission.

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.[6] 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. By dramatically increasing total daily pill burden for PWH, polypharmacy related to heart failure can also increase the risk of non-adherence to ART.[2] In Alvi et al's longitudinal study of PWH who use drugs, patients prescribed 5+ pills per day, including ART and non-ART medications, were half as likely to be adherent to their ART as those prescribed 4 pills or fewer (OR 0.54, 95% CI 0.40-0.72).[1] GDMT comprises at least 4 pills, placing patients at high risk for non-adherence even if they use single-tablet ART and no other medications.[1] In turn, non-adherence is associated with hospital readmissions and increased mortality, as well as increased HIV viral load and risk of forward transmission. Pill burden and pill fatigue can manifest as spotty adherence or "drug holidays," with serious implications for ART resistance patterns and HIV prevention.

8.5 PRELIMINARY STUDIES: Briefly summarize any preliminary studies relevant to your proposed research (space limit: one half page):

Despite compelling evidence that pill burden negatively impacts adherence, there is no combination pill for HFrEF available in the US, in part due to unclear commercial incentives. The standard 4-drug regimen for HFrEF comprises 2 inexpensive generics costing less than $10/month (a beta blocker and spironolactone), and 2 brand-name medications that both exceed $500/month (an SGLT2 inhibitor and twice-daily sacubitril-valsartan). SGLT2 inhibitors and sacubitril-valsartan are manufactured by different companies, which lack a clear financial incentive to compound their medication with inexpensive generics.

Over-encapsulation represents an inexpensive, efficient way to combine tablets into a single capsule for HFrEF, reducing total daily pill burden for patients with HIV cardiomyopathy. Over-encapsulated combination therapies have improved outcomes in other cardiovascular conditions, and can be used to evaluate the impact of combination therapy as groundwork for manufacturing a combination tablet. Polypills have proven to be a feasible and effective intervention to improve medication adherence in low-resource settings. A trial of 303 patients in Alabama employed over-encapsulation methods to combine medications for cholesterol and hypertension into a single capsule.[7] The investigators found over-encapsulation to be feasible, affordable, and acceptable to patients, and the polypill resulted in significantly lower systolic blood pressure and cholesterol.[7] Polypills have also been shown to improve adherence and reduce mortality in patients with a history of myocardial infarction (MI).[8] In the 2022 SECURE trial, a polypill was associated with a 33% relative reduction in mortality among patients with a recent MI.[8]

All once-daily HFrEF medications can be packaged into a single small capsule (Supplemental Figure), reducing patients' pill burden while avoiding the manufacturing and financial hurdles that have prevented a HFrEF polypill from coming to market. There is another single-center study of a HFrEF polypill currently recruiting in Houston, Texas, using similar over-encapsulation methods in a general HFrEF population.[9] If these early studies are successful, a HFrEF polypill intervention could be continued at ZSFG, and replicated for other HIV-associated comorbidities. Furthermore, SGLT2 inhibitors will go off-patent in 2025. If polypills are shown to improve clinical outcomes, generic manufacturers or public payors, such as California's Medi-Cal Rx, would have incentive to manufacture a generic HFrEF combination tablet.

8.6 * TREATMENT PROTOCOL: Is this a treatment study, i.e. does this study intend to provide treatment to individuals with a medical or psychological condition: (REQUIRED)

(•) Yes ( ) No

8.7 * BILLABLE PROCEDURES: Does this study involve any procedures, lab tests or imaging studies that have a CPT code and could be billable to patients, their insurance, Medi-Cal, Medicare, or any other entity (answer 'Yes' even if the study is going to pay for all the procedures): (REQUIRED)

(•) Yes ( ) No

8.8 * COMMON RESEARCH ACTIVITIES: Types of research activities that will be carried out. Check all that apply and describe in more detail in the 'Procedures / Methods' section: (REQUIRED)

- [x] Interviews, questionnaires, surveys
- [ ] Educational or cognitive tests
- [ ] Focus groups
- [ ] Social media-based research activities
- [ ] Observation
- [ ] Fitness tests or other exertion activities
- [ ] Use of mobile health apps or other apps
- [ ] Collection of data from wearable tech such as Fitbit, Apple Watch, Garmin, motion actigraphs, etc.)
- [x] Non-invasive imaging or testing (MRI, EEG, pulse oximetry, etc.)
- [ ] Imaging procedures or treatment procedures that involve radiation (x-rays, CT scans, CT-guided biopsies, DEXA scans, MUGA or PET scan)
- [ ] Administration of contrast agent
- [x] Randomization to one intervention versus another

- [ ] Use of placebo
- [ ] Biopsy conducted solely for research purposes
- [ ] Sham surgical procedure
- [ ] None of the above

8.9 * PROCEDURES / METHODS: (REQUIRED)

For clinical research, list all study procedures, tests and treatments required for this study, including when and how often they will be performed. If there are no clinical procedures, describe the research activities.

If some of the activities would occur even if the person were not in the study, as in the case of treatment or tests performed for diagnostic purposes, **clearly differentiate between those activities that will be done solely for research purposes and those that are happening as part of routine care.**

Examples may include:

- additional scans outside standard clinical diagnosis or monitoring
- additional biopsies to collect tissue for research
- extra clinic visits
- extra lab tests not required for clinical care

If you have a procedure table, attach it to the submission with your other study documents.

Aim 1 (qualitative; separate IRB # 22-38189). Conduct formative interviews of patients, pharmacists, HIV primary care and infectious disease providers, and cardiologists to characterize barriers to medication adherence and elicit perspectives on a HFrEF polypill to reduce total daily pill burden among PWH.

Aim 2 (the focus of this CHR application). Investigate whether over-encapsulation of several heart failure medications into a single capsule ("polypill") is feasible and improves adherence among 20-40 adults with HFrEF, with or without HIV, using a single-center, crossover RCT design.
Hypothesis: Compared with usual care, a HFrEF polypill implementation strategy will increase adherence to GDMT 4 weeks and reduce total daily pill burden among patients with HFrEF.
Rationale:HFrEF among PWH is associated with a high pill burden, which adversely impacts adherence. Over-encapsulation is an inexpensive and replicable method to co-package several tablets into a single capsule at the level of the pharmacy. However, the role of over-encapsulation to reduce pill burden among adults with HIV and HFrEF is unknown.
Design: Pilot phase II open-label randomized trial with a 2x2 crossover design (AB/BA)
Recruitment:The research team will identify potential participants using existing clinical lists within our divisions (the Epic Heart Failure registry, the cardiology and Ward 86 clinic lists, and the cardiology and family medicine inpatient lists). DPH clinicians (i.e. cardiovascular clinical pharmacist Christina Wang) will pre-approve the use of Epic reports or Epic lists of potential participants prior to contacting them for recruitment for the study. Customized columns in Epic lists (for example, age, renal function, HIV status, contact information) will be used to screen potentially eligible participants without opening their chart. In some cases, researchers may want to open the patient's chart to review their eligibility prior to contacting the patient for recruitment & consent. In these cases, researchers will get approval from the patient's own healthcare provider prior to opening their chart to screen for study eligibility.
Eligibility: Participants will be eligible if they are ≥ 18 years old and carry a diagnosis of heart failure, with prior chart evidence of reduced ejection fraction (i.e., prior echocardiogram or MRI with ejection fraction ≤50%). Given that our pharmacy partner in this over-encapsulation study is Daniel's Pharmacy, we will only include participants who can conveniently obtain their medications through one of 3 available mechanisms (mail, pick up at a ZSFG clinic, or pick up at Daniel's pharmacy). At an initial screening visit (week T-1), participants will be asked to provide

informed consent. Their current heart failure regimen will be reviewed. If they are not prescribed all four classes of GDMT, and do not have contraindications, additional agents will be prescribed by the study clinician if determined to be clinically appropriate.
At the first trial visit (week 0), labs will be checked if clinically indicated after starting new medications. Additional guideline-directed medications may be started if there are no contraindications. During this visit, participants will be randomized to the AB group or BA group using REDcap. The run-in period will consist of the screening visit and the first trial visit (week 0). Potential participants who do not attend these two initial visits will not be enrolled in the trial and will not receive the intervention. The goal of this is to ensure that patients who start the intervention are likely to present for follow-up, especially given the importance of monitoring patients for safety metrics and medication-related adverse effects.
Intervention: The intervention will be pharmacy-level over-encapsulation of once-daily heart failure medications (beta-blocker, SGLT2 inhibitor, spironolactone, and ACE/ARB/ARNI) into a single capsule. For some patients, other once-daily cardiovascular medications, such as a diuretic, may be included if capsule size allows (otherwise, these medications will continued to be filled separate to the polypill, as individual tablets). If the patient uses a twice-daily ARNI medication, the morning dose may be included in the polypill and the PM dose will continue to be dispensed separately. We will partner with Daniel's Pharmacy, a local community pharmacy with proficiency in over-encapsulation and over 20 years' experience working with ZSFG to deliver adherence interventions.
Polypill Description:
For patients in the polypill arm, heart failure medications will be filled as usual, but rather than dispensing each medication separately, the pharmacy technician will hand-pack all once-daily heart failure medications into a small plastic capsule (Supplemental Figure). The doses will be individualized to the patient based on their physician's prescription. Thus, the polypill will be a late-stage implementation intervention to reduce pill burden, without restricting dose possibilities or interfering with medication titration. We are requesting an IND exempt determination from the UCSF IRB, given that the proposed intervention involves repackaging of FDA-approved medications without significantly changing their risk profile nor seeking additional indications (see the Drugs section of this application). This is similar to an IND exemption received by co-investigator Dr. Mark Huffman for the NHLBI-funded QUARTET-USA trial of a hypertension polypill.
Visit Schedule and Randomization:
Patients will first attend an intake visit (week T-1), where eligibility will be reviewed, informed consent will be obtained, baseline labs and patient questionnaires will be collected, and additional GDMT agents may be prescribed by the study clinician if clinically indicated and there are no contraindications. As part of the consent, we will also ask participants' permission to contact their primary outpatient providers. For participants that have a medication support person (e.g. a home nurse, building nurse or adult family member who manages their medications), we will ask permission to contact that person during the study period to ensure safe transitions in medication doses or packaging.
At the first trial visit (week 0), labs will be rechecked if clinically indicated, and additional GDMT agents may prescribed if clinically indicated, with the goal of all participants being prescribed guideline-directed quad therapy for HFrEF prior to randomization if there are no contraindications.[11] The study team will also check if the participant has any video conferencing capability (WhatsApp, FaceTime, or Zoom) to facilitate virtual pill counts, and if not, the study team will offer to help the participant set this up. The study team will send a message to the patient's primary outpatient providers in order to update the care team with any medication changes and to create a line of communication for any issues or concerns that may arise. Study participants will be encouraged to contact the study team with any issues specifically related to their heart failure medications during the study period, and to contact their regular doctors about any other clinical concerns. If the study team is contacted about other issues (e.g. new heart failure symptoms), we will conduct clinical triage and refer the participant to the ER, urgent care, and/or their primary doctors as clinically indicated.
During the first trial visit (week 0), half of participants will be randomized to the AB group (polypill for 4 weeks, then individual tablets for 4 weeks). The other half of participants will be randomized to the BA group (individual tablets for 4 weeks, then polypill for 4 weeks). This follow-up period is comparable to that of the pilot crossover trial that preceded QUARTET-USA (4 weeks in a polypill arm and 4 weeks in a placebo arm).
After randomization, participants assigned to receive the polypill up-front will be delivered 30-day supplies of the polypill via their preferred delivery method (mail, pick up at a ZSFG clinic, or pick up at Daniel's Pharmacy). Participants assigned to usual care will be mailed or pick up their existing heart failure medications as individual pills. The screening visit and first trial visit may be timed by study clinicians based on when the participant's heart failure medications will be ready for a refill according to insurance.
At trial follow-up visits at 4 and 8 weeks, participants will be assessed for outcomes and adverse events and will undergo lab monitoring as clinically indicated. Patients will be asked to bring in their pill bottles and/or MediSets or bubble packs. Please see the attached Schedule of Study Visits. Medication doses may be titrated at these visits if clinically indicated. Participants in the AB

and BA arms will have the same follow-up schedule, and can opt to receive refills of their medications by mail, at the pharmacy, or in clinic. Any new starts of guideline-directed heart failure medications that are included in the polypill will be continued as individual pills when the polypill group crosses over to the individual tablet condition, and/or when the trial concludes. All participants will be referred to cardiology clinic, if not already established there, for ongoing management of their heart failure therapies after the trial.
Participants will receive $10 gift certificates for each visit, with an additional $30 if they bring in their pill bottles and an additional $10 if blood draws are needed. Bus tokens, parking vouchers, or other transportation vouchers will also be provided. At the conclusion of the study, we will perform semi-structured exit interviews with participants, clinicians, and pharmacists. We will use prepared interview guides, and will offer $20 reimbursement for participation in a 30-60 minute exit interview. We will elicit stakeholders' experiences with the polypill, barriers encountered, preferences for trade-offs between pill size and number of pills, perceptions about taking polypills vs. the individual components, and experience working with the pharmacy for medication delivery.
Outcomes: The primary outcome will be adherence to overall and individual components of GDMT at 4 and 8 weeks, as measured by pill count. If participants do not bring their pill bottles to the visit, we will try to reschedule within the next few days before the 30-day supply is completed. If it is not possible to reschedule, the study team will ask to have a video chat with the patient (FaceTime, WhatsApp or Zoom) in order to complete a virtual pill count over video call. If none of these are possible, the primary outcome will not be collected for that time point. Secondary outcomes will include number of evidence-based heart failure therapies prescribed, number of dose increases or achieved doses of heart failure therapies, MMAS-8 adherence questionnaire, self-reported adherence to GDMT and other medications, treatment satisfaction using the Treatment Satisfaction Questionnaire for Medication, and documented episodes of treatment-related adverse effects (e.g. allergy, hyperkalemia, or bradycardia). We will also capture feasibility metrics in conjunction with Daniel's Pharmacy, including production time and costs for polypill packaging. As a pilot trial, our study will not be powered for clinical outcomes, but key exploratory outcomes will include HFrEF admissions, change in BNP or NT-ProBNP (a measure of clinical heart failure status), blood pressure, heart rate, and change in health-related quality of life measured by the Kansas City Cardiomyopathy Questionnaire. The exit interviews will be transcribed, coded, and analyzed using the CFIR Framework for evaluation of an implementation project.
In addition to the in-person study visits (screening, 0, 4, and 8 weeks), we will perform telephone visits with participants at approximately 2 and 6 weeks. At these telephone check-ins, we will screen for adverse events and order monitoring labs if clinically indicated according to the study team's discretion.
Clinical Tests and Treatments: At monthly follow-up visits, we will monitor standard vital signs (heart rate, blood pressure, and oxygen saturation) and standing weight, as is routine for a cardiology clinic visit. Participants will also undergo lab monitoring at least every 2 months or as clinically indicated, including a basic metabolic panel to monitor potassium and creatinine levels while on heart failure medications. We will also measure a BNP or NT-proBNP at baseline, 4 weeks, and 8 weeks (laboratory measure of heart failure status).
Exit interviews: We will conduct 30-60 minute semi-structured exit interviews, using interview guides prepared using the Consolidated Framework for Implementation Research. Qualitative data will be audiotaped and transcribed verbatim using Qualtranscribe or secure Zoom or OneDrive transcription services. Dedoose software will be used to assist the investigative team with organizing, coding, and analyzing the qualitative data. The de-identified transcribed data will then be available for team members for coding and analysis. The coding team for interviews will consist of Dr. Colette DeJong and Dr. Matthew Durstenfeld from UCSF, Dr. Justin Chen and Dr. Anubha Agarwal from Washington University in St. Louis, and one research assistant, with mentorship from Drs. Priscilla Hsue and Wayne Steward. We will deploy a Framework Analysis approach to analyze our data.
Limitations: Our study is designed as a small pilot trial, and thus, will not be powered for clinical outcomes such as heart failure admissions. Our primary outcomes are feasibility and adherence. Adherence can be challenging to measure; however, we will use well-validated tools including pill counts and the MMAS-8 questionnaire. We selected a crossover trial design because it allows for efficient comparison of treatment arms in a small study population, and because the use of each participant as his/her own matched control will minimize unmeasured confounders. This study design carries risk of carryover effects, wherein participants remain impacted by the prior treatment after crossing over. Since one arm is standard delivery of medications as individual tablets, we expect that these carryover effects will be minimal, and we will include treatment order as a variable in our regression models.

Data and Samples to be Collected:

Blood draw: Standard venipuncture will be performed on patients with < 10ml taken at each blood draw. Patients will undergo serial potassium and creatinine monitoring, as well as BNP or NT-proBNP monitoring.

Study follow-up: participants will complete monthly follow-up visits with Dr. DeJong or a clinical research assistant (weeks 0, 4, and 8). At these visits, they will be asked to provide their medication supply for pill count, and will be screened for any treatment-related adverse effects. They will also be asked to complete the MMAS-8 questionnaire for adherence, the Treatment Satisfaction Questionnaire for Medication, and the Kansas City Cardiomyopathy Questionnaire for treatment-related quality of life among people with heart failure. As described above, participants will also complete telephone visits (weeks 2 and 6) to assess self-reported adherence and screen for adverse events.

Medical Record Review: We will review participants' Epic-based medical records for comorbidities, medications, total daily pill burden, blood pressure, heart rate, and hospitalizations.

8.10 * STANDARD CLINICAL PRACTICE: To what extent, if any, do the planned research procedures differ from the care that people would otherwise receive at this institution or the study site if not being done locally: (REQUIRED)

The main difference from standard clinical practice is the over-encapsulation of GDMT into a single capsule, which will be a pharmacy-level packaging intervention (similar to a bubble pack). We hypothesize that this will reduce pill burden, improve treatment satisfaction, and improve adherence to heart failure therapies with proven mortality benefit. There are additional ways that this could impact care, which will be actively monitored by the pilot trial's investigators:

1. Prior to randomization, participants who are not already prescribed guideline-directed quad therapy for HFrEF (beta blocker, SGLT2 inhibitor, MRA, and ACE/ARB/ARNI) will be initiated on these therapies at starting doses if no contraindications exist over the course of the first study visits. These therapies have proven mortality benefit in heart failure, and are part of guideline-directed care. Simultaneous or rapid-sequence initiation of these therapies with close monitoring is encouraged in expert consensus.[11] Thus, all participants will be escalated to a guideline-directed HFrEF regimen prior to randomization, and in this way will undergo a form of intensified usual care.
2. More tablets may be cut in half in order to fit into a small capsule (for example, a half-tab of metoprolol succinate 100mg, rather than a whole tab of metoprolol succinate 50mg). This type of substitution is often performed at the pharmacy according to their formulary. Only pills that are explicitly allowed to be cut in half by the FDA would be split for the purposes of the study.
3. Like a bubble pack, this is primarily a packaging intervention, with individualization of patients' medication regimen and dosing. However, there may be some scenarios in which there is a minor medication change in order to accommodate the polypill intervention, if considered safe and clinically low-risk by the study clinician. These could include minor dose adjustments (for example, switching an SGLT2 inhibitor from 10mg daily to 12.5mg daily, if required by capsule size and covered by the patient's insurance; switching from metoprolol to comparable doses of a similar drug, bisoprolol, which has smaller pill size and is more amenable to the polypill intervention; or converting from twice-daily carvedilol to once-daily carvedilol extended release). At time of study consent, we will ask participants for permission to make small medication or dose adjustments for the purposes of the polypill intervention, with close monitoring and notification of their primary outpatient team. From our clinical experience, these adjustments have low risk of harm. Furthermore, participants will be monitored with at least monthly visits, which is more frequent than the typical standard of care, in addition to regular lab monitoring. This potential change and associated risks will be explained to participants as part of the informed consent process.

The follow-up schedule also differs from usual care, in that participants will be seen at least once a month for the duration of the study. As described above, participants will attend monthly follow-up visits, which is at the upper limit of normal for heart failure management (in clinical care, patients are usually seen every 2-6 weeks while GDMT is being titrated, and then every 3-6 months once they are on stable doses). At these visits, standard vital signs (heart rate, blood pressure, and oxygen saturation) and standing weight will be monitored, and patients will be screened for heart failure symptoms and medication side effects, as is routine for a cardiology clinic visit. Participants will also undergo regular lab monitoring, including a basic metabolic panel, as clinically indicated or at least every 2 months. This is a typical interval for patients whose GDMT is being actively titrated, but is more frequent than standard clinical are for patients on stable doses of GDMT (typical lab monitoring every 3-6 months).

8.11 * INSTRUMENTS: List all questionnaires, surveys, interview, or focus group guides that will be used

for this study: (REQUIRED)

Surveys:

- MMAS-8 Questionnaire (published and validated)
- Treatment Satisfaction Questionnaire for Medication (published and validated)
- Kansas City Cardiomyopathy Questionnaire (published and validated)
- Patients will be asked to self-report adherence to their medications, using a survey adapted from the Basic Medications Questionnaire (see Self-Reported Adherence Questionnaire as an attachment)

Exit interviews:

- Health professional interview guide
- Patient interview guide
- Community pharmacy partner interview guide

Attach any unpublished instruments in the 'Other Study Documents' section of the Initial Review Submission Packet form after completing the study application. Published instruments should NOT be attached.

8.12 * BIOSPECIMEN COLLECTION: Are you drawing any blood or collecting other biosamples (e.g. tissue, buccal swabs, urine, saliva, hair, etc.) for analysis under this protocol and/or storage for future research: (REQUIRED)

(•) Yes ( ) No

* Could this study generate genetic data that may be broadly shared (e.g., submitted to NIH in compliance with **Genomic Data Sharing (GDS)/Genome-Wide Association Studies (GWAS)** requirements): **(REQUIRED)**

( ) Yes (•) No

Based on current research trends, we strongly recommend including the genomic data sharing language in the consent form to allow future sharing, even if you don't anticipate it now. It's easier to add it now than trying to reconsent all the specimen donors!

8.13 * STATISTICAL METHODS: Briefly summarize the methods and types of analyses that will be performed: (REQUIRED)

Quantitative outcomes:
Demographic data for participants will be described in each group and compared using a Student' s T-test (continuous variables) or Fisher's exact test (categorical variables). We will use mixed model multilevel linear regression analyses to determine the effect of a polypill vs. usual care on the primary outcome (GDMT adherence) and secondary outcomes (including adherence ratio to ART, self-report of GDMT and other medication adherence using the MMAS-8 questionnaire, treatment satisfaction using the Treatment Satisfaction Questionnaire for Medication, and documented episodes of adverse effects related to GDMT use). We will report descriptive data pertaining to feasibility metrics, including production time and costs for polypill packaging. Analyses will be performed according to an intention-to-treat principle, using Stata, version 17. The threshold for statistical significance will be $P < 0.05$.

Qualitative outcomes (exit interviews):
We will deploy a Framework Analysis approach to analyze our data. Members of the research team will read the transcripts several times to familiarize themselves with the text. Transcripts will be analyzed using deductive and inductive content analysis simultaneously. Members of the research team will develop a codebook after reviewing the transcripts. The resulting codebook will include codes reflecting topics from the interview guide, in addition to previously unexpected

topics identified inductively. The draft coding scheme will be reviewed by the study team and reconciled by consensus. When the codebook is finalized, members of the research team will organize participants' responses by the corresponding codes with support and guidance from co-investigators. Common themes will be developed inductively, synthesizing participants' responses across codes to reflect the themes. Coded transcript data will be charted into a framework matrix to facilitate the identification of themes around GDMT adherence and the pilot trial of an over-encapsulated HFrEF polypill. The study team will then present these themes to the in-depth interview participants to confirm they represent the participant's perspectives (member checking).

8.14 * REFERENCES: List only the 5-10 most relevant references (a separate bibliography can be attached for reference purposes if this study involves novel approaches, agents, or an emerging technology that the IRB may not be familiar with): (REQUIRED)

1. Mohd Salleh NA, Richardson L, Kerr T, et al. A Longitudinal Analysis of Daily Pill Burden and Likelihood of Optimal Adherence to Antiretroviral Therapy Among People Living With HIV Who Use Drugs. *J Addict Med*. 2018;12(4):308-314. doi:10.1097/ADM.0000000000000403
2. Krentz HB, Cosman I, Lee K, Ming JM, Gill MJ. Pill Burden in HIV Infection: 20 Years of Experience. *Antivir Ther*. 2012;17(5):833-840. doi:10.3851/IMP2076
3. Tan JY, Greene M, Blat C, et al. Examining the Impact of the Golden Compass Clinical Care Program for Older People with HIV: A Qualitative Study. *AIDS Behav*. 2022;26(5):1562-1571. doi:10.1007/s10461-021-03509-0
4. Alvi RM, Afshar M, Neilan AM, et al. Heart failure and adverse heart failure outcomes among persons living with HIV in a US tertiary medical center. *Am Heart J*. 2019;210:39-48. doi:10.1016/j.ahj.2019.01.002
5. Greene SJ, Khan MS. Quadruple Medical Therapy for Heart Failure. *J Am Coll Cardiol*. 2021;77(11):1408-1411. doi:10.1016/j.jacc.2021.02.006
6. Bassi NS, Ziaeian B, Yancy CW, Fonarow GC. Association of Optimal Implementation of Sodium-Glucose Cotransporter 2 Inhibitor Therapy With Outcome for Patients With Heart Failure. *JAMA Cardiol*. 2020;5(8):948-951. doi:10.1001/jamacardio.2020.0898
7. Muñoz D, Uzoije P, Reynolds C, et al. Polypill for Cardiovascular Disease Prevention in an Underserved Population. *N Engl J Med*. 2019;381(12):1114-1123. doi:10.1056/NEJMoa1815359
8. Castellano JM, Pocock SJ, Bhatt DL, et al. Polypill Strategy in Secondary Cardiovascular Prevention. *N Engl J Med*. 2022;387(11):967-977. doi:10.1056/NEJMoa2208275
9. Pandey, A. Polypill Strategy for Heart Failure With Reduced Ejection Fraction. Clinical Trial Identifier: NCT04633005. Available at https://www.clinicaltrials.gov/ct2/show/NCT04633005.
10. Castellano JM, Sanz G, Peñalvo JL, et al. A Polypill Strategy to Improve Adherence: Results From the FOCUS Project. *J Am Coll Cardiol*. 2014;64(20):2071-2082. doi:10.1016/j.jacc.2014.08.021
11. Greene SJ, Butler J, Fonarow GC. Simultaneous or rapid sequence initiation of quadruple medical therapy for heart failure—optimizing therapy with the need for speed. JAMA cardiology. 2021 Jul 1;6(7):743-4.

9.0 Biospecimen Collection and/or Bank Administration

9.1 * TYPE OF SPECIMENS (check all that apply): (REQUIRED)

- [x] Blood (provide amount below)
- [ ] Tissue (describe below)
- [ ] Other type of biospecimen, such as sputum, cerebrospinal fluid, buccal swabs, etc. (describe below)
- [ ] Existing/archival materials (name source below)

Briefly describe the types of biospecimens that will be collected. Provide the amount of blood, if applicable. For leftover/existing/archival material, identify the source:

A basic metabolic panel will be collected when determined by the study team to be clinically indicated, or at least once every 4 weeks. At these visits, less than 10cc of blood will be collected. We will also measure either a BNP or NT-ProBNP as an exploratory clinical outcome at baseline, 4 weeks, and 8 weeks. Assuming a maximum of 5 blood collections per patent (weeks 0, 2, 4, 6, 8), less than 50cc of blood total will be collected over the course of the study.

9.3 * SPECIMENS ARE: (check all that apply): (REQUIRED)

- [ ] Leftover specimens from a clinical diagnostic or therapeutic procedure
- [x] Specimens collected for research purposes only (including extra samples taken during a clinical procedure)
- [ ] Other

9.5 * FUTURE SPECIMEN USE: Will any specimens or portions of specimens be retained after the study is over for possible use in future research studies: (REQUIRED)

- ○ Yes
- ◉ No

9.7 * SPECIMEN DESTINATION: Indicate where specimens will ultimately be stored: (REQUIRED)

Outside Entities: Indicate where specimens will be sent if they will not remain at UCSF (choose at least one; check all that apply):

- [ ] Cooperative group bank
- [ ] NIH
- [ ] Other university or collaborator
- [ ] Industry sponsor
- [x] Other
- [x] N/A - all specimens will remain at UCSF

Specify to what institution, cooperative group, or company specimens will be transferred:

NT-ProBNP is a sendout test at ZSFG, performed by ARUP laboratories.

Internal Storage: If specimens will remain at UCSF, in what kind of facility will they reside (choose at least one; check all that apply):

- [ ] UCSF repository/bank being established under this protocol
- [ ] Existing UCSF specimen repository/bank with IRB approval
- [ ] National cooperative group bank housed at UCSF
- [x] Other location at UCSF (please describe)
- [ ] N/A - no specimens will be retained at UCSF facilities

Please provide the name of the department, the program, and the physical location where the specimens will be housed. If the specimens will be stored in an already established bank, provide the name of the bank and its iRIS approval number.:

Samples will be collected at ZSFG in either the clinical laboratory or the research laboratory at 5B. If needed, study samples will be transported by the study team from 5B to the clinical lab for processing, and/or securely stored prior to being sent to ARUP laboratories for processing of NT-ProBNP.

9.8 SPECIMENS SENT OUTSIDE UCSF - IDENTIFIABILITY: Will direct identifiers be associated with specimens or shared with other researchers and/or outside entities:

- ◉ Yes
- ○ No
- ○ N/A - Specimens will not be shared with others

If **Yes**, which identifiers will be sent with specimens:

- [x] Name
- [x] Date of birth
- [x] Specimen collection dates
- [ ] Social Security number
- [x] Medical record number
- [ ] Address
- [ ] Phone number
- [ ] Email address
- [ ] Other dates (surgery date, clinic visit dates, etc.)

Provide a justification for sending direct identifiers with the specimens:

ARUP laboratories is a partner of ZSFG and processes all NT-ProBNP samples for the hospital. If needed, we will send NT-ProBNP samples to ARUP laboratories in accordance with ZSFG procedures established by the clinical laboratory and research laboratory (5B).

9.9 * CLINICAL FOLLOW-UP DATA: Will clinical follow-up data be linked to specimens (i.e., will medical record information continue to be abstracted after the specimen is collected): (REQUIRED)

- (•) Yes
- ( ) No

Provide duration of follow-up or 'indefinitely':

The duration of the pilot trial period (approximately 2 months)

9.10 * UCSF-BANKED SPECIMENS - LINKING AND SHARING OF IDENTIFIERS: (REQUIRED)

- [ ] Samples are completely de-identified before being added to the bank/repository. There is no way to link the specimens back to the subjects.
- [ ] Samples are coded and researchers are able to link the specimens to specific subjects.
- [x] Samples are stored with direct identifiers in the repository.

Explain under what circumstances identifiers may be released with specimens or say 'None' if identifiers will **NEVER** be released with specimens:

We will coordinate with the ZSFG clinical and research laboratory in order to process research specimens (i.e., basic metabolic panel or BNP). We will request that laboratory results are uploaded to ZSFG Epic if possible, since these results are clinically useful in the management of patients with HFrEF. We may securely store samples with identifiers (name, MRN, DOB) prior to sending samples to ARUP laboratories for sendout tests, i.e. NT-ProBNP.

9.11 UCSF-BANKED SPECIMENS – IDENTIFIERS: List the identifiers that will be collected, stored, or linked with the specimens:

- [x] Name
- [x] Date of birth
- [ ] Social Security number
- [x] Medical record number
- [ ] Address
- [ ] Phone number
- [ ] Email address
- [ ] Other dates (dates of surgery, visit dates)

9.12 DISTRIBUTION: Specimens banked at UCSF may be made available to (check all that apply):

- [ ] UCSF researchers
- [ ] Non-UCSF researchers
- [ ] Industry
- [x] None of the above - specimens will be retained and used within our own research program

9.13 UTILIZATION REVIEW: Is there a formal utilization review process for distribution of specimens:

(•) Yes ( ) No

Describe the process:

Our study participants will be getting some labs that are part of routine clinical care (e.g. checking a metabolic panel after starting a guideline-directed heart failure medication). These labs will be billed to insurance through the standard clinical laboratory. The participants will also get some labs solely for the purpose of the study (e.g. baseline lab tests prior to the intervention); these will be paid for by the study. This will be managed in accordance with ZSFG research laboratory processes, by either 1) collecting the specimens at the 5B research laboratory or 2) using the standard clinical laboratory and billing the study instead of insurance. We will work with the ZSFG clinical research service to adhere to all relevant processes and procedures.

10.0 Drugs and Devices

10.1 * DRUGS AND/OR BIOLOGICS: Are you STUDYING any drugs and/or biologics that are either approved or unapproved: (REQUIRED)

(•) Yes ( ) No

If you have questions about FDA requirements for drug or device research, you can send an email to request a consult.

10.2 LIST THE DRUGS OR BIOLOGICS: List the drugs or biologics that will be studied. In the drug details screen you will be asked questions such as:

- **Whether the drug or biologic is FDA approved**
- **If the drug or biologic will be provided at no cost**
- **If an IND is necessary, the IND number, and who holds the IND**
- **If the drug or biologic is FDA approved and an IND is not required, the rationale for the decision**
- **If the Investigational Drug Service (IDS) is dispensing the drug or biologic (required unless a waiver is obtained from the IDS)**

Please see the UCSF IRB website for more details about the use of drugs and biologics in research, including the IND Decision Worksheet. Verification of IND numbers: If the sponsor's protocol does not list the IND number, you must submit documentation from the sponsor or FDA identifying the IND number for this study. Attach this documentation in the Other Study Documents section of the Initial Review Submission Packet. If you have any correspondence from the FDA or sponsor regarding this drug or biologic, please attach it to the application.

View Details	Drug Name	FDA Approved	A new drug or a new use of an already approved drug:	IND Number
⊟	**Trade Drug Name:** Jardiance **Generic Drug Name:** empagliflozin **Investigational Drug Name:**	Yes	Yes	

Trade Drug Name:	Jardiance
Generic Drug Name:	empagliflozin
Investigational Drug Name:	
Identify the name of the manufacturer or source of investigational drug/biologic:	Boehringer Ingelheim
Is the drug supplied at no cost?	No
Is the Drug FDA Approved:	Yes
Is this a new drug or a new use of an already approved drug	Yes
Is an IND necessary	No
IND Number	
Who holds the IND:	N/A
IND details:	
If FDA Approved and an IND is not required, Please provide a rationale for exemption:	The polypill will be a late-stage packaging intervention to reduce pill burden, without restricting dose possibilities or interfering with medication titration. All medications included will be used for FDA-approved indications at standard dosing. We are requesting that the UCSF IRB make an IND Exempt determination, and have attached the IND Decision worksheet. Our collaborator Dr. Mark Huffman similarly received an IND exempt determination for an over-encapsulated polypill for hypertension (QUARTET-USA, NCT03640312).
Are you currently using this IND in another research project?	No
If yes, list the IRB Number(s):	
Will the investigational pharmacy be dispensing?	No
If the source is not a FDA licensed facility, provide details regarding the purity, quality, stability and sterility of the investigational drug/biologic:	

⊟	**Trade Drug Name:** Dapagflozin **Generic Drug Name:** **Investigational Drug Name:**	Yes	Yes	

Trade Drug Name:	Dapagflozin
Generic Drug Name:	
Investigational Drug Name:	
Identify the name of the manufacturer or source of investigational drug/biologic:	AstraZeneca
Is the drug supplied at no cost?	No
Is the Drug FDA Approved:	Yes
Is this a new drug or a new use of an already approved drug	Yes

Is an IND necessary	No
IND Number	
Who holds the IND:	N/A
IND details:	
If FDA Approved and an IND is not required, Please provide a rationale for exemption:	Please see above
Are you currently using this IND in another research project?	No
If yes, list the IRB Number(s):	
Will the investigational pharmacy be dispensing?	No
If the source is not a FDA licensed facility, provide details regarding the purity, quality, stability and sterility of the investigational drug/biologic:	

⊟	**Trade Drug Name:** METOPROLOL SUCCINATE **Generic Drug Name:** METOPROLOL SUCCINATE **Investigational Drug Name:**	Yes	Yes	

Trade Drug Name:	METOPROLOL SUCCINATE
Generic Drug Name:	METOPROLOL SUCCINATE
Investigational Drug Name:	
Identify the name of the manufacturer or source of investigational drug/biologic:	Generic
Is the drug supplied at no cost?	No
Is the Drug FDA Approved:	Yes
Is this a new drug or a new use of an already approved drug	Yes
Is an IND necessary	No
IND Number	
Who holds the IND:	N/A
IND details:	
If FDA Approved and an IND is not required, Please provide a rationale for exemption:	Please see above
Are you currently using this IND in another research project?	No
If yes, list the IRB Number(s):	
Will the investigational pharmacy be dispensing?	No
If the source is not a FDA licensed facility, provide details regarding the purity, quality, stability and sterility of the investigational drug/biologic:	

⊟	**Trade Drug Name:** SPIRONOLACTONE **Generic Drug Name:** SPIRONOLACTONE **Investigational Drug Name:**		Yes	Yes	

Trade Drug Name:	SPIRONOLACTONE
Generic Drug Name:	SPIRONOLACTONE
Investigational Drug Name:	
Identify the name of the manufacturer or source of investigational drug/biologic:	Generic
Is the drug supplied at no cost?	No
Is the Drug FDA Approved:	Yes
Is this a new drug or a new use of an already approved drug	Yes
Is an IND necessary	No
IND Number	
Who holds the IND:	N/A
IND details:	
If FDA Approved and an IND is not required, Please provide a rationale for exemption:	Please see above
Are you currently using this IND in another research project?	No
If yes, list the IRB Number(s):	
Will the investigational pharmacy be dispensing?	No
If the source is not a FDA licensed facility, provide details regarding the purity, quality, stability and sterility of the investigational drug/biologic:	

⊟	**Trade Drug Name:** EPLERENONE **Generic Drug Name:** EPLERENONE **Investigational Drug Name:**		Yes	Yes	

Trade Drug Name:	EPLERENONE
Generic Drug Name:	EPLERENONE
Investigational Drug Name:	
Identify the name of the manufacturer or source of investigational drug/biologic:	Generic
Is the drug supplied at no cost?	No
Is the Drug FDA Approved:	Yes
Is this a new drug or a new use of an already approved	Yes

drug	
Is an IND necessary	No
IND Number	
Who holds the IND:	N/A
IND details:	
If FDA Approved and an IND is not required, Please provide a rationale for exemption:	Please see above
Are you currently using this IND in another research project?	No
If yes, list the IRB Number(s):	
Will the investigational pharmacy be dispensing?	No
If the source is not a FDA licensed facility, provide details regarding the purity, quality, stability and sterility of the investigational drug/biologic:	

⊟	**Trade Drug Name:** BISOPRODOL FUMARATE **Generic Drug Name:** BISOPROLOL FUMARATE **Investigational Drug Name:**	Yes	Yes	

Trade Drug Name:	BISOPRODOL FUMARATE
Generic Drug Name:	BISOPROLOL FUMARATE
Investigational Drug Name:	
Identify the name of the manufacturer or source of investigational drug/biologic:	Generic
Is the drug supplied at no cost?	No
Is the Drug FDA Approved:	Yes
Is this a new drug or a new use of an already approved drug	Yes
Is an IND necessary	No
IND Number	
Who holds the IND:	N/A
IND details:	
If FDA Approved and an IND is not required, Please provide a rationale for exemption:	Please see above
Are you currently using this IND in another research project?	No
If yes, list the IRB Number(s):	
Will the investigational pharmacy be dispensing?	No
If the source is not a FDA licensed facility, provide details regarding the purity, quality,	

stability and sterility of the investigational drug/biologic:				

⊟	**Trade Drug Name:** LISINOPRIL **Generic Drug Name:** LISINOPRIL **Investigational Drug Name:**	Yes	Yes	

Trade Drug Name:	LISINOPRIL
Generic Drug Name:	LISINOPRIL
Investigational Drug Name:	
Identify the name of the manufacturer or source of investigational drug/biologic:	Generic
Is the drug supplied at no cost?	No
Is the Drug FDA Approved:	Yes
Is this a new drug or a new use of an already approved drug	Yes
Is an IND necessary	No
IND Number	
Who holds the IND:	N/A
IND details:	
If FDA Approved and an IND is not required, Please provide a rationale for exemption:	See above
Are you currently using this IND in another research project?	No
If yes, list the IRB Number(s):	
Will the investigational pharmacy be dispensing?	No
If the source is not a FDA licensed facility, provide details regarding the purity, quality, stability and sterility of the investigational drug/biologic:	

⊟	**Trade Drug Name:** LOSARTAN **Generic Drug Name:** LOSARTAN POTASSIUM **Investigational Drug Name:**	Yes	Yes	

Trade Drug Name:	LOSARTAN
Generic Drug Name:	LOSARTAN POTASSIUM
Investigational Drug Name:	
Identify the name of the manufacturer or source of investigational drug/biologic:	Generic
Is the drug supplied at no cost?	No
Is the Drug FDA Approved:	Yes

Is this a new drug or a new use of an already approved drug	Yes
Is an IND necessary	No
IND Number	
Who holds the IND:	N/A
IND details:	
If FDA Approved and an IND is not required, Please provide a rationale for exemption:	See above
Are you currently using this IND in another research project?	No
If yes, list the IRB Number(s):	
Will the investigational pharmacy be dispensing?	No
If the source is not a FDA licensed facility, provide details regarding the purity, quality, stability and sterility of the investigational drug/biologic:	

⊟	**Trade Drug Name:** **Generic Drug Name:** **Investigational Drug Name:**	VALSARTAN VALSARTAN	Yes	Yes	

Trade Drug Name:	VALSARTAN
Generic Drug Name:	VALSARTAN
Investigational Drug Name:	
Identify the name of the manufacturer or source of investigational drug/biologic:	Generic
Is the drug supplied at no cost?	No
Is the Drug FDA Approved:	Yes
Is this a new drug or a new use of an already approved drug	Yes
Is an IND necessary	No
IND Number	
Who holds the IND:	N/A
IND details:	
If FDA Approved and an IND is not required, Please provide a rationale for exemption:	See above
Are you currently using this IND in another research project?	No
If yes, list the IRB Number(s):	
Will the investigational pharmacy be dispensing?	No
If the source is not a FDA	

licensed facility, provide details regarding the purity, quality, stability and sterility of the investigational drug/biologic:	

⊟	**Trade Drug Name:** Entresto **Generic Drug Name:** sacubitril /valsartan **Investigational Drug Name:**	Yes	No	

Trade Drug Name:	Entresto
Generic Drug Name:	sacubitril/valsartan
Investigational Drug Name:	
Identify the name of the manufacturer or source of investigational drug/biologic:	Novartis
Is the drug supplied at no cost?	No
Is the Drug FDA Approved:	Yes
Is this a new drug or a new use of an already approved drug	No
Is an IND necessary	No
IND Number	
Who holds the IND:	N/A
IND details:	
If FDA Approved and an IND is not required, Please provide a rationale for exemption:	The polypill will be a late-stage packaging intervention to reduce pill burden, without restricting dose possibilities or interfering with medication titration. All medications included will be used for FDA-approved indications at standard dosing. We are requesting that the UCSF IRB make an IND Exempt determination, and have attached the IND Decision worksheet. Our collaborator Dr. Mark Huffman similarly received an IND exempt determination for an over-encapsulated polypill for hypertension (QUARTET-USA, NCT03640312).
Are you currently using this IND in another research project?	No
If yes, list the IRB Number(s):	
Will the investigational pharmacy be dispensing?	No
If the source is not a FDA licensed facility, provide details regarding the purity, quality, stability and sterility of the investigational drug/biologic:	

⊟	**Trade Drug Name:** COREG CR **Generic Drug Name:** CARVEDILOL PHOSPHATE **Investigational Drug Name:**	Yes	No	

Trade Drug Name:	COREG CR
Generic Drug Name:	CARVEDILOL PHOSPHATE

Investigational Drug Name:	
Identify the name of the manufacturer or source of investigational drug/biologic:	Generic
Is the drug supplied at no cost?	No
Is the Drug FDA Approved:	Yes
Is this a new drug or a new use of an already approved drug	No
Is an IND necessary	No
IND Number	
Who holds the IND:	N/A
IND details:	
If FDA Approved and an IND is not required, Please provide a rationale for exemption:	The polypill will be a late-stage packaging intervention to reduce pill burden, without restricting dose possibilities or interfering with medication titration. All medications included will be used for FDA-approved indications at standard dosing. We are requesting that the UCSF IRB make an IND Exempt determination, and have attached the IND Decision worksheet. Our collaborator Dr. Mark Huffman similarly received an IND exempt determination for an over-encapsulated polypill for hypertension (QUARTET-USA, NCT03640312).
Are you currently using this IND in another research project?	No
If yes, list the IRB Number(s):	
Will the investigational pharmacy be dispensing?	No
If the source is not a FDA licensed facility, provide details regarding the purity, quality, stability and sterility of the investigational drug/biologic:	

⊟	**Trade Drug Name:** **Generic Drug Name:** **Investigational Drug Name:**	CARVEDILOL CARVEDILOL	Yes	Yes	

Trade Drug Name:	CARVEDILOL
Generic Drug Name:	CARVEDILOL
Investigational Drug Name:	
Identify the name of the manufacturer or source of investigational drug/biologic:	Generic
Is the drug supplied at no cost?	No
Is the Drug FDA Approved:	Yes
Is this a new drug or a new use of an already approved drug	Yes
Is an IND necessary	No
IND Number	

Who holds the IND:	N/A
IND details:	
If FDA Approved and an IND is not required, Please provide a rationale for exemption:	IND determination was previously provided by the IRB for the use of an empty capsule to copackage several common heart failure medications. We are maintaining the accuracy of this list by adding carvedilol (the short acting version of Coreg CR). Other cardiovascular medications, not on this list, may be copackaged in the capsule if capsule size permits.
Are you currently using this IND in another research project?	No
If yes, list the IRB Number(s):	
Will the investigational pharmacy be dispensing?	No
If the source is not a FDA licensed facility, provide details regarding the purity, quality, stability and sterility of the investigational drug/biologic:	

10.3 * MEDICAL DEVICES: Are you STUDYING any medical devices, in vitro diagnostics, or assays that are either approved or unapproved:(REQUIRED)

○ Yes ◉ No

If you have questions about FDA requirements for drug or device research, you can send an email to request a consult.

10.6 * EXPANDED ACCESS: Is this an expanded access or compassionate use protocol, meaning the primary purpose is to diagnose, monitor or treat a patient's condition, rather than the collection of safety and efficacy data of the experimental agent: (REQUIRED)

○ Yes ◉ No

11.0 Sample Size and Eligibility Criteria

11.1 * ENROLLMENT TARGET: How many people will you enroll: (REQUIRED)

51

If there are multiple participant groups, indicate how many people will be in each group:

PATIENTS: n = 20-40
In this crossover trial, participants will be randomized in 1:1 fashion into the AB group (polypill followed by usual care), or the BA group (usual care followed by polypill). Given that this is a small pilot feasibility study, actual sample size will be modified in accordance with actual logistical constraints.

CLINICIANS: n = 4-8
We will conduct exit interviews with nurses (n = 1-2), pharmacists (n = 1-2), and ZSFG prescribers (n = 2-4) to discuss their observations of the intervention.

DANIEL'S PHARMACY STAFF: n = 3
We will observe pharmacy technicians and clinical pharmacists (n = 2-3) at our community partner, Daniel's Pharmacy, in order to collect feasibility metrics, i.e., time and cost of producing

the polypill. We will also conduct exit interviews with these community pharmacy partners (n = 2-3) to discuss their experience with the polypill intervention.

11.3 * SAMPLE SIZE JUSTIFICATION: Explain how and why the number of people was chosen. For multi-site studies, this is referring to the number that will be enrolled across all sites: (REQUIRED)

In the FOCUS trial of an over-encapsulated polypill for hypertension, patients randomized to a polypill were 24% more likely to be adherent compared to those receiving separate pills (50.8% adherence in polypill group vs. 41% adherence in usual care, p = 0.019; OR, 1.24; 95% CI, 1.06-1.47).[10] Considering a power of 80% and alpha of 5%, using a two-treatment crossover trial design, a minimum sample size of 20 participants total (10 per arm) will be necessary to identify a 20% absolute change in adherence ratio among patients prescribed the polypill vs. usual care, assuming a standard deviation of 30% in the change in adherence ratio over time. Assuming that up to 50% of patients will not complete the run-in period, we estimate that 40 patients (20 per arm) should be recruited. However, as described above, this is primarily a feasibility pilot study and the sample size may be modified in response to logistical constraints.

For the exit interviews with healthcare professionals, we will recruit approximately 4-8 HCPs at ZSFG (nurses, pharmacists, and prescribers) as well as approximately 2-3 community pharmacists or pharmacy technicians at Daniel's Pharmacy. If theoretical saturation is not reached, additional HCPs who interfaced with the intervention can be recruited for exit interviews.

11.4 * PARTICIPANT AGE RANGE: Eligible age ranges: (REQUIRED)

- [ ] 0-6 years
- [ ] 7-12 years
- [ ] 13-17 years
- [x] 18-64 years
- [x] 65+

11.5 * STUDY POPULATIONS: Data will be collected from or about the following types of people (check all that apply): (REQUIRED)

- [x] Inpatients
- [x] Outpatients
- [ ] Family members or caregivers
- [x] Providers
- [ ] People who have a condition but who are not being seen as patients
- [ ] Healthy volunteers
- [ ] Students
- [x] Staff of UCSF or affiliated institutions
- [x] None of the above

11.6 * SPECIAL SUBJECT GROUPS: Check the populations that may be enrolled: (REQUIRED)

- [ ] Children / Minors
- [ ] Adult subjects unable to consent for themselves
- [ ] Adult subjects unable to consent for themselves (emergency setting)
- [ ] Subjects with diminished capacity to consent
- [ ] Subjects unable to read, speak or understand English
- [ ] Pregnant women
- [ ] Fetuses
- [ ] Neonates
- [ ] Prisoners
- [x] Economically or educationally disadvantaged persons
- [ ] None of the above

If not already addressed in the Background and Significance questions in the Research Plan section or elsewhere, explain why it is appropriate to include the types of subjects checked above in this particular study:

Our study is based at ZSFG, which serves an economically disadvantaged patient population. This is also the population that we hope would benefit most from a combination pill for heart failure, since patients who are economically or socially disadvantaged face higher barriers to adherence to a complex, 4-drug regimen. Our study will also focus on a specific population of patients with HIV and HFrEF, who have high pill burden and face unique barriers to medication adherence. Single-pill combination therapies for HIV greatly expanded access to ART in this population; however, there are no combination therapies available for most cardiac conditions, which now comprise a majority of pill burden for many PWH at ZSFG.

Describe the additional safeguards that have been included in the study to protect the rights and welfare of these subjects and minimize coercion or undue influence:

Here are some examples:

- evaluating capacity to consent for individuals who may be decisionally impaired (specify how)
- calibrating payment amounts to be non-coercive for the financially disadvantaged
- conducting more in-depth evaluations of subjects' understanding of the study and the voluntary nature of participation
- involving advocates in the consent process

More information and other safeguards are described here: **Vulnerable Subject Populations** and **Recruiting Staff and Students**.

After reviewing patient eligibility, patients will be given an overview of the study by a coordinator or other study team member. All questions will be answered to his/her satisfaction prior to providing verbal consent for participation. To minimize coercion, the research team will make sure the patients know the study is voluntary and choosing to participate or not will not affect their care. If the patient agrees to participate, the coordinator will arrange a time to schedule the interview.

11.7 * INCLUSION CRITERIA: Briefly describe the population(s) that will be involved in this study. Include anyone that data will be collected from or about (e.g. patients, healthy controls, caregivers, providers, administrators, students, parents, family members, etc.): (REQUIRED)

PATIENT PARTICIPANTS:

- Age ≥ 18 years old
- Previously diagnosed with heart failure with reduced ejection fraction (≤50% on most recent echocardiogram or cardiac MRI), ACCF/AHA stage C or D, NYHA class II-IV
- With or without a prior diagnosis of HIV (HIV+ and HIV- subgroups)
- Able to conveniently obtain medications through one of 3 available mechanisms (mail, pick up at a ZSFG clinic, or pick up at Daniel's pharmacy)
- Last eGFR > 30
- Working telephone number for telephone follow-up

CLINICIANS RECRUITED FOR EXIT INTERVIEWS:

- Nurses, pharmacists, patient care navigators, or prescribers who work at ZSFG in the Ward 86 or cardiology clinics
- Observed or interfaced with the polypill trial at ZSFG

DANIEL'S PHARMACY STAFF:

- Pharmacy technicians or clinical pharmacists employed at Daniel's Pharmacy, who have direct participation in polypill preparation and packaging

11.8 * EXCLUSION CRITERIA: List any exclusion criteria (e.g. reasons why someone would not be included in the study): (REQUIRED)

PATIENTS:

- Patients who are not fluent in English. These patients are excluded from this small pilot trial for feasibility reasons (e.g. access to medical interpreters for the consent process and exit interviews), however, we plan to include these patients in a larger subsequent trial.
- Patients who have dementia or lack capacity
- Patients who are incarcerated
- Patients who cannot provide informed consent
- Patients with a ventricular assist device (VAD) or patients with an MI, unstable angina, stroke, or TIA within 12 weeks prior to enrollment
- Women who are pregnant, breastfeeding or of childbearing potential and are not using and do not plan to continue using medically acceptable form of contraception throughout the study (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.

CLINICIANS:

- Clinicians who are co-investigators on the proposed study
- Those who have not cared for patients enrolled in the polypill trial, or otherwise interfaced with the polypill intervention at ZSFG

DANIEL'S PHARMACY STAFF:

- Those who have not had hands-on experience with polypill packaging and preparation

11.9 * RESEARCH CONDUCTED ON PATIENT CARE WARDS: Do any study activities take place on any patient care units including inpatient wards, peri- or post-operative care units, operating rooms, or in the Emergency Department at UCSF Health medical facilities: (REQUIRED)

○ Yes ◉ No

11.11 * EMERGENCY DEPARTMENT: Does your protocol or study involve any of the following patient related activities in the emergency department (e.g. subject identification, recruitment, consent, blood draws, specimen retrieval, involvement of ED staff (nursing, tech, and/or physician), or any other ED based procedures): (REQUIRED)

○ Yes ◉ No

12.0 Recruitment and Consent

12.1 * COMPETITIVE ENROLLMENT: Is this a competitive enrollment clinical trial? By competitive enrollment, we mean that sites who do not enroll participants early may not get to participate at all: (REQUIRED)

○ Yes ◉ No

12.2 * SUBJECT IDENTIFICATION METHODS: What kinds of methods will be used to identify potential participants for recruitment (check all that apply): (REQUIRED)

- [x] Review of patients' conditions, history, test results, etc. (includes patients seen in clinic, scheduled for surgery, a procedure, imaging, or tests, or seen in the Emergency Department as well as searching through medical record data for possible cohort identification)
- [ ] Already approved recruitment registry
- [x] Re-contact of participants from the investigators' previous studies
- [ ] Referrals from colleagues (attach the 'Dear Colleague' letter or other recruitment materials you will provide to colleagues)
- [ ] Referrals from the community / word of mouth
- [ ] Advertisements (flyers, brochures, radio or t.v. ads, posting on clinical research sites or social media, presentation of the study at community events/media, etc.)
- [ ] Online recruiting tool (describe below)
- [ ] CTSI Recruitment Services unit
- [ ] Posting on UCSF Clinical Trials, ClinicalTrials.gov or other publicly available clinical trial website
- [x] Other method (describe below)

* Provide details about the subject identification methods: **(REQUIRED)**

Patients will be identified as potential study candidates by the investigator, co-investigator or research coordinator through one of the following mechanisms:

1) Prior studies: Patients from a prior qualitative study (IRB # 22-38189) who expressed interest in a HFrEF polypill pilot trial and consented to further contact will be asked if they would like to participate.

2) Clinical lists, with approval from a DPH clinician: The research team will identify potential participants using existing clinical lists within our divisions (the Epic Heart Failure registry, the cardiology and Ward 86 clinic lists, and the cardiology and family medicine inpatient lists). The ZSFG heart failure registry is a clinical tool within Epic that was co-developed by Dr. Jonathan Davis (co-investigator on the present study) and is used for heart failure panel management and quality improvement at ZSFG. Recruitment through the ZSFG heart failure registry will allow us to identify potential participants who are not currently connected to the cardiology clinic, and thus, may serve to benefit more from medication titration using a polypill strategy. DPH clinicians (i.e. cardiovascular clinical pharmacist Christina Wang) will pre-approve the use of Epic reports or Epic lists, such as the HFrEF registry list, prior to contacting participants for recruitment for the study. Customized columns in Epic lists and data fields in Epic reports (for example, age, renal function, HIV status, contact information) will be used to screen potentially eligible participants without opening their chart. In some cases, researchers may want to open the patient's chart to review their eligibility prior to contacting the patient for recruitment & consent. In these cases, researchers will get approval from the patient or from the patient's own healthcare provider prior to opening their chart to screen for study eligibility.

3) Provider referrals: we will present at providers' meetings and request referrals from ZSFG clinicians in cardiology, general medicine and Ward 86.

4) Fliers: if needed to meet recruitment goals, we will post study fliers in patient waiting rooms, specifically in the Ward 86 and/or cardiology outpatient areas. See attached flier draft.

Clinicians and Daniel's Pharmacy staff will be identified as candidates for exit interviews by a member of the research team. Lists or groups of clinicians will be approved by a DPH clinician prior to contact for study recruitment. As described in the inclusion criteria, we will recruit clinicians and Daniel's Pharmacy staff who interfaced with the polypill intervention for exit interviews to learn more about their experience with the polypill. We will also observe some members of Daniel's Pharmacy staff preparing the polypill in order to gather feasibility metrics (time and cost of production).

* Did all the participants of previous studies provide permission to be contacted for future studies: **(REQUIRED)**

(•) Yes ( ) No

12.3 * SEARCHING OF MEDICAL RECORDS: (REQUIRED)

Whose patients are they:

- [x] Investigators' own patients or patients seen within the same practice
- [x] Patients not under the care of the investigators

How and by whom will records be accessed and searched (check all that apply):

- [x] Self-search in APeX or other medical records source
- [ ] Self-search using UCSF's Research Cohort Selection Tool
- [ ] CTSI Consultation Service Recruitment Services
- [ ] UCSF Academic Research Services (ARS)
- [ ] University of California Research Exchange (UC ReX)
- [ ] Other method (describe below)

12.4 * DETERMINATION OF ELIGIBILITY: How, when, and by whom will eligibility for recruitment be determined: (REQUIRED)

As described above, the research team will identify potential participants from provider referrals, patient self-referrals, prior study participants who agreed to future contact, or existing clinical lists within our divisions (the Epic Heart Failure registry, the cardiology and Ward 86 clinic lists, and the cardiology and family medicine inpatient lists). The ZSFG heart failure registry is a clinical tool within Epic that was co-developed by Dr. Jonathan Davis (co-investigator on the present study) and is used for heart failure panel management and quality improvement at ZSFG. Recruitment through the ZSFG heart failure registry will allow us to identify potential participants who are not currently connected to the cardiology clinic, and thus, may serve to benefit more from medication titration using a polypill strategy. DPH clinicians (i.e. cardiovascular clinical pharmacist Christina Wang) will pre-approve the use of Epic reports or Epic lists, such as the HFrEF registry list, prior to contacting participants for recruitment for the study. Customized columns in Epic lists and data fields in Epic reports (for example, age, renal function, HIV status, contact information) will be used to screen potentially eligible participants without opening their full chart. In some cases, researchers may want to open the patient's chart to review their eligibility prior to contacting the patient for recruitment & consent. In these cases, researchers will get approval from the patient or from the patient's own healthcare provider prior to opening their chart to screen for study eligibility.

As part of the initial recruitment call, the study team may ask some pre-screening questions to determine if the patient meets inclusion criteria prior to arranging an in-person visit. If this information is already known from a referring clinician or from Epic lists, these pre-screening questions may be skipped. These questions pertain to pill-taking practices (e.g. use of a pill box or MediSet) and do not include any questions about diagnoses or medical history. These pre-screening questions are listed below and also in the revised telephone script:

"In order to see if you might be eligible for this study, can I ask you a few screening questions?

- Do you currently use a bubble pack or pillbox?
- Does anyone help you with your medications?
- Out of the past week, how many days do you think you took all of your medications? Have you ever had difficulty taking all of your medications?

If patient does not meet criteria:
Based on this information, this study is not quite right for you, but hopefully there will be another study in the future that is a better fit. Thank you so much for your time today. Have a good day!"

Specifically, participants would be excluded from the study if they use a bubble pack or if they have someone who helps administer all of their medications. Potential participants who report

perfect adherence will be excluded from initial recruitment efforts, given that we are preferentially recruiting those who miss some doses of their medication; however, they may be included at a later time depending on recruitment targets.

Daniel's Pharmacy staff will be approached for recruitment in exit interviews if they were involved in manufacturing the polypill. ZSFG clinicians will be contacted for exit interviews if they cared for patients receiving the polypill intervention. A DPH clinician will approve groups of possible HCP participants prior to contacting them.

12.5 * INITIATION OF CONTACT: Who initiates contact (check all that apply): (REQUIRED)

- [x] Investigators/study team
- [ ] UCSF recruitment unit (e.g. CTSI Consultation Services)
- [x] Potential participant
- [ ] Other (explain below)

12.6 * HOW IS CONTACT INITIATED: (check all that apply): (REQUIRED)

- [x] In person
- [x] Phone
- [x] Letter / email
- [ ] Website or app
- [ ] Other (explain below)

Attach the telephone recruitment script in the Other Study Documents section of the Initial Review Submission Packet Form. If potential participants will initiate contact, attach the telephone screening script that will be used to provide more information about the study and determine if callers are eligible to participate.

Attach the recruitment letter or email template in the Other Study Documents section of the Initial Review Submission Packet Form.

12.7 RECRUITMENT PLAN: Based on the checkboxes you chose above, please provide a narrative describing your recruitment plan. We want to know:

- **Who is conducting the search for potential participants, and how?**
- **How are potential subjects being approached for recruitment? By whom, and when?**

If there will be more than one participant group (e.g. patients, healthy controls, caregivers, family members, providers, etc.), provide details about the recruitment plans for each group. (Recommended length - 100-250 words)

After reviewing patient eligibility with the PI or co-PI, and in accordance with the processes described above, contact with patients will be initiated by a trained study investigator or staff member. Contact will be initiated in-person or by telephone.

The patient will be given an overview of the study by a coordinator or other study team member. All questions will be answered to his/her satisfaction prior to providing written consent for participation. To minimize coercion, the research team will make sure the patients know the study is voluntary and choosing to participate or not will not affect their care. If the patient agrees to participate, the coordinator will arrange a time to schedule an intake visit. The process to recruit participants will be led and coordinated by trained study team members.

Contact with Daniel's Pharmacy staff members will be initiated in-person. Contact with ZSFG clinicians will be initiated in-person or by email; please see the attached ZSFG clinician email recruitment script.

12.8 * CONSENT METHODS: How will permission to participate (i.e., informed consent) be obtained from

each potential participant. If there will be multiple groups and different plans for consenting each, check all that apply. See the orange Help bubble to the right for more detailed guidance. Participants will (check all that apply): (REQUIRED)

- [x] Sign a paper consent form at the end of the consent discussion (signed consent)
- [x] Sign an electronic consent form using DocuSign or REDCap's e-signature function (signed consent)
- [ ] Provide online unsigned consent through an app, a website, or a survey tool such as Qualtrics or REDCap (waiver of signed consent)
- [ ] Be told about the study and be given a handout/information sheet and be asked if they agree to participate (verbal consent - waiver of signed consent)
- [ ] Complete the study activities and turn in materials, as in the case of a completed survey that is placed in a drop box or mailed to the study team (implied consent - waiver of signed consent)
- [ ] Not be able to provide consent and will have a family member consent for them, as in the case of a critically ill or unconscious patient (surrogate consent)
- [ ] Not able to provide consent (emergency medicine, greater than minimal risk waiver/alteration of consent - requires an approved community consultation plan)
- [ ] Not able to provide consent (emergency medicine, minimal risk waiver/alteration of consent)
- [ ] Not know about the study, as in the case of chart reviews or observations of public behavior (waiver of consent)
- [ ] Other method (describe below)

Attach your consent form, information sheet, or electronic consent text in the Informed Consent Documents section of the Initial Review Submission Packet Form.

If this study is FDA-regulated (i.e., involves investigational drugs or devices, or approved drugs or devices for investigational uses) and you want to use DocuSign or REDCap to collect research signatures, you must use an FDA-compliant version of DocuSign or REDCap. More information is available at FAQ #2. For the FDA-compliant version of DocuSign, submit an access request at https://ucsf.service-now.com/ucsfit and contact it-cloudapps@ucsf.edu with questions. For the FDA-compliant version of REDCap ("REDCap Premium"), go to https://redcap-prem.ucsf.edu and contact Academic Research Systems Support with questions.

12.9 * CONSENT PROCESS: Describe the process for obtaining informed consent, including details such as who will have the consent discussion and when participants will be asked to sign the consent form in relation to finding out about the study: (REQUIRED) We encourage researchers to review our guidance on obtaining and documenting informed consent.

- **If there are multiple groups being consented differently, provide details about the consent process for each group.**
- **If you are relying on verbal or implied consent, provide details about how that will happen.**
- **For studies using online recruitment and consent or consent via mail, provide details here.**

We will obtain informed consent from participants prior to their participation in the pilot trial using paper, Docusign or Redcap. Please see the attached consent documents. As part of the consent process, potential participants will be provided a description of the study, including the potential risks of participation. Patients will be clearly informed that their participation or responses will not affect their access to ongoing care at ZSFG cardiology clinics. ZSFG clinicians and Daniel's Pharmacy Staff who are recruited to participate in the exit interviews will be informed that their participation is optional. Any data collected will be stored in a de-identified manner and secured

on a password protected server. Participants may choose to withdraw from the study at any point. Along with explicitly outlining of the study procedures, potential participants will be informed that they may choose to withdraw from the study at any point. Prior to consenting, participants will have an opportunity to ask any questions they may have. In addition to consenting to the pilot study, we will ask participants for consent to be contacted about related studies that they may be eligible for in the future. Patients who do not speak English will be excluded from the study. Only trained employees at UCSF will consent participants and manage protected health information (PHI) or personally identifiable data.

* It is important that the people obtaining consent are qualified to do so. Briefly describe the training and experience these individuals have in obtaining informed consent: **(REQUIRED)**

All study team members have experience and certification for conduct of Human Subjects Research and have satisfied basic Collaborative Institutional Training Initiative (CITI) and Good Clinical Practice training requirements. Dr. Hsue's research group has extensive experience conducting clinical research at ZSFG in both inpatient and outpatient settings. As the senior investigator on the study, Dr. Hsue will oversee the consent processes and ensure that informed consent is obtained in accordance to ZSFG and UCSF CHR standards.

12.10 * CONSENT COMPREHENSION: Indicate how the study team will assess and enhance the subjects' understanding of study procedures, risks, and benefits prior to signing the consent form (check all that apply): (REQUIRED) Tip: Review the Consent Comprehension - Learning Notes in the Help bubble at the right for specific questions that can be asked to assess comprehension, consider using the UCSF Decision-Making Capacity Assesment Tool, and review our guidance on obtaining written or verbal informed consent for more detail on how to conduct the assessment.

- [x] The study team will engage the potential participant in a dialogue, using open-ended questions about the nature of the study or the experimental treatment, the risks and benefits of participating, and the voluntary nature of participation
- [x] Potential participants will be asked or shown a series of questions to assess their understanding of the study purpose, procedures, risks and benefits, as well as the voluntary nature of participation (especially appropriate when the consent process happens online or through a mobile health app)
- [ ] Other method (describe below):

Provide details of the other approaches that will be used, if using another method to assess comprehension:

12.14 TIME: What is the estimated time commitment for participants (per visit and in total):

PATIENTS:

The estimated on-site time commitment for participants, not including travel to and from ZSFG, will be approximately 5 hours:

- Consent visit (30 minutes)
- Intake visit (60 minutes)
- 5 study follow-up visits (30 minutes each): study week 0, 4, and 8 in--person and weeks 2 and 6 by telephone
- Exit interview (60 minutes)

In addition, participants will continue taking their heart failure medications (individually packaged vs. polypill) on a daily basis.

CLINICIANS:
The time commitment for clinician exit interviews will be approximately 1 hour.

DANIEL'S PHARMACY STAFF:
The time commitment for pharmacy staff exit interviews will be approximately 1 hour. We will also conduct on-site observation of pharmacy staff at 2-3 visits in order to collect feasibility metrics about the time and cost of polypill production. During these site visits, the pharmacy staff will continue with their regular activities.

IMPORTANT TIP: Ensure this information is consistent with the information provided in the consent form.

12.15 ALTERNATIVES: Is there a standard of care (SOC) or usual care that would be offered to prospective participants at UCSF (or the study site) if they did not participate in this research study:

(•) Yes ( ) No

Describe the care that patients would ordinarily receive at the medical center if they did not participate in this study (provide details, assuming that some of the IRB members are not specialists in this field):

Patients who choose not to participate in the pilot trial will continue to receive standard care for their heart failure diagnosis, including all of the guideline-directed medications discussed above. The study intervention is co-packaging these medications into a single capsule for ease of use. If patients choose not to participate, they will continue to receive these medications, but they will be dispensed individually by the pharmacy.

12.16 OFF-STUDY TREATMENT: Is the study drug or treatment available off-study:

( ) Yes
(•) No
( ) Not applicable

13.0 Waiver of Consent/Authorization for Recruitment Purposes

This section is required when medical records may be reviewed to determine eligibility for recruitment.

13.1 * PRACTICABILITY OF OBTAINING CONSENT PRIOR TO ACCESS: Study personnel need to access protected health information (PHI) during the recruitment process and it is not practicable to obtain informed consent until potential subjects have been identified: (REQUIRED)

(•) Yes

If **no**, a waiver of consent/authorization is NOT needed.

13.2 * RISK TO PRIVACY: A waiver for screening of health records to identify potential subjects poses no more than minimal risk to privacy for participants:

(•) Yes

If **no**, a waiver of authorization can NOT be granted.

13.3 * RIGHTS/WELFARE: Screening health records prior to obtaining consent will not adversely affect subjects' rights and welfare:

(•) Yes

If **no**, a waiver of authorization can NOT be granted.

13.4 * IDENTIFIERS: Check all the identifiers that will be collected prior to obtaining informed consent:

- [x] Names
- [ ] Dates
- [ ] Postal addresses
- [x] Phone numbers
- [ ] Fax numbers
- [ ] Email addresses
- [ ] Social Security Numbers*
- [x] Medical record numbers
- [ ] Health plan numbers
- [ ] Account numbers
- [ ] License or certificate numbers
- [ ] Vehicle ID numbers
- [ ] Device identifiers or serial numbers
- [ ] Web URLs
- [ ] IP address numbers
- [ ] Biometric identifiers
- [ ] Facial photos or other identifiable images
- [ ] Any other unique identifier
- [ ] None

Note: HIPAA rules require that you collect the minimum necessary.

13.5 * HEALTH INFORMATION: Describe any health information that will be collected prior to obtaining informed consent:

Since our study topic is a combination pill for patients wit HFrEF, with a specific interest in patients with concomitant HIV, our inclusion criteria specifies adults over 18 who carry an existing diagnosis of HFrEF (EF <40%) with or without a prior diagnosis of HIV. We will rely on existing diagnoses, and we will not do any new testing to screen for study eligibility. To identify eligible participants, we will conduct targeted chart review on patients presenting to ZSFG cardiology clinics, the Positive Health Program and the ZSFG cardiology inpatient service. We will not collect any additional health information prior to obtaining informed consent, other than reviewing the chart for eligibility.

Note: HIPAA requires that you collect the minimum necessary.

13.6 * DATA RETENTION/DESTRUCTION PLAN: Describe your plan to destroy any identifiable data collected to determine eligibility for recruitment. This should be done at the earliest opportunity. If you plan to retain identifiable recruitment data, provide the justification for doing so:

All data collected for study recruitment will be destroyed as soon as study recruitment has concluded.

14.0 Risks and Benefits

14.1 RESEARCH-RELATED RISKS: Check if your study involves any of these specific research-related risks to participants that may need to be disclosed in the consent form:

- [x] For interventional studies, risk that the regimen may be more harmful or less effective than other available interventions
- [ ] Risks associated with radiation exposure for imaging studies specifically for research purposes
- [ ] Risks associated with the administration of contrast agent for imaging studies
- [ ] Risks associated with withholding of treatment or discontinuation of current treatment (e.g., washout period is required by the study protocol)
- [x] For randomized, placebo-controlled trials, possible temporary or permanent health consequences from the deprivation of effective therapies during the placebo administration

period

- ☐ For studies involving a sham surgical procedure, the risk that participants may experience increased morbidity without the possibility of benefit
- ☐ Risks associated with modification or extension of a surgical procedure primarily for research purposes (e.g. risks associated with prolonging anesthesia, time in the operating room, etc.)
- ☐ Risk of pain or physical discomfort caused by the research intervention
- ☐ Possible personal discomfort due to sensitive topics (stress, embarassment, trauma)

* For any boxes checked above, describe how you will minimize these risks and discomforts, e.g., adding or increasing the frequency of monitoring, additional screening to identify and exclude people with diminished kidney or liver function, or modification of procedures such as changing imaging studies to avoid giving contrast agent to people who are more likely to suffer side effects from it, etc.: **(REQUIRED)**

Since we are studying a packaging intervention of standard, FDA-approved therapies for heart failure, we anticipate that excess risk as a result of participation in our study will be low. However, heart failure therapies themselves carry risk including hypotension, hyperkalemia, and acute kidney injury. Participants may have increased exposure to these guideline-directed therapies due to either 1) new or higher-dose prescriptions from the study team, or 2) increased adherence to medications that are already prescribed. We will mitigate these risks by 1) excluding patients with contra-indications to heart failure guideline-directed medical therapies (GDMT), including advanced chronic kidney disease (eGFR <30), medication allergy, or pregnancy; and 2) maintaining an above-average follow-up schedule with at least monthly study visits. At these visits, patients will be screened for any adverse events, which will be reviewed by the research team. Any serious events will be reported to CHR and the study sponsor.

14.2 * RISKS: Describe any anticipated risks and discomforts not listed above: (REQUIRED)

The following are possible risks of participation in this study. Overall we believe that this study meets the regulatory definition of minimal risk, i.e., "the probability and magnitude of harm or discomfort anticipated in the research are not greater than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." We base this determination on the fact that participants will be prescribed guideline-directed, FDA-approved drugs at standard doses for heart failure. Current expert opinion supports starting several medication classes simultaneously or in rapid sequence for patients with heart failure (e. g. **https://jamanetwork.com/journals/jamacardiology/fullarticle/2777813**). All participants will be prescribed GDMT if not already prescribed and no contraindications exist. The intervention is primarily a packaging intervention, akin to the use of a bubble pack or MediSet to promote medication-taking adherence. The risk of side effects from these medications are not significantly different than if the medications were prescribed simultaneously outside of a research setting.

Potential risks to participants are described below:

Pilot trial:

- Adverse effects of HFrEF medications: We hypothesize that over-encapsulation of HFrEF medications will lead to increased adherence to these medications among the intervention group. Patients may have increased exposure to these guideline-directed therapies due to either 1) intensification or uptitration of their regimen by the study team, or 2) increased adherence due to the polypill intervention. Increased utilization of these beneficial medications may also be associated with increased rates of documented adverse reactions. Adverse reactions to GDMT include hypotension, bradycardia, medication allergy, or hyperkalemia, which requires lab monitoring with any dose adjustment. To mitigate these risks, we will screen patients for contraindications at time of enrollment, and evaluate patients for adverse drug reactions at each follow-up visit. We will perform routine lab monitoring on participants, including evaluating for hyperkalemia.
- Possible dose adjustment of some heart failure medications: The standard dose of SGLT2 for heart failure is one tablet of 10mg daily, however, some healthcare systems including the San Francisco VA prescribe a half-tablet of 25mg (i.e. 12.5mg daily). This difference is not thought to be clinically significant, and depends on the institution and formulary. In our prototyping, we found that only empagliflozin or dapagliflozin 12.5mg can be accommodated by the capsules. Thus, at time of study consent, we would ask participants for permission to adjust their SGLT2 dose from 10mg to 12.5mg daily if necessary. Similarly, some patients may be transitioned between clinically similar classes of beta

blocker at comparable doses (i.e., from metoprolol succinate to bisoprolol due to pill size; or, from carvedilol twice-daily to carvedilol once-daily to be included in the polypill). From our clinical experience, these changes have minimal chance of harm, given that these changes will be between comparable agents at similar doses. However, there is a minimal risk that this slightly higher dose may increase side effects, which can include low blood pressure or low heart rate (beta blockers) or urinary frequency and dehydration (SGLT2 inhibitor). To mitigate this risk, we will first confirm with the participant's primary cardiologist and/or primary care provider that this adjustment is likely to be safe. Participants will then be monitored with at least monthly visits and lab monitoring, which is more frequent than the typical standard of care. They will also be provided a study contact phone number in case of any medication-related adverse effects. The potential risk of empagliflozin side effects will be explained in detail to participants as part of the consent process.

- Co-packaging and/or repackaging heart failure medications: As with bubble packs, changing packaging of prescription medications carries risk of medication error. We will partner with a pharmacy with experience in medication repackaging, and adhere to California State Board of Pharmacy regulations with regards to labeling and inclusion of prescription information. Daniel's Pharmacy frequently prepares bubble packs and MediSets for heart failure patients at ZSFG, which involves co-packaging individual tablets. As with these bubble packs, the polypills will be prepared by trained pharmacy technicians, and will undergo secondary review by a clinical pharmacist for accuracy before being delivered to the patient.
- Use of half-tablets: Some tablets may be cut in half by the pharmacist prior to inclusion in the poly-capsule. In compliance with U.S. Pharmacopeia General Chapter 795, half-tablets should be used within 6 months of pill cutting. This will be clearly labelled on the pill bottle and conveyed to study participants.
- Impact on adherence to excluded HFrEF medications: Any twice-daily HFrEF medications, such as sacubitril/valsartan, will have a second dose (e.g. the evening dose) which is omitted from the polypill and will continue to be dispensed individually. It is possible that this may change patients' perceptions of cardiovascular medications that are not included in the polypill, or negatively impact adherence to those medications. At time of enrollment, we will discuss with patients that only some HFrEF tablets will be over-encapsulated, and reinforce the importance of all prescribed medications. We will monitor adherence to all HFrEF medications, antiretroviral therapy, and other prescriptions throughout the study period. Since total daily pill burden is a driver of non-adherence, we hypothesize that the polypill intervention will positively impact adherence to all prescriptions.
- Risk of medication error during crossover: At time of crossover, participants will switch from a polypill to individual tablets, or vice versa. This could carry a risk of taking double doses of some medications if they continue to take both dosage forms at once (e.g., continue to take some GDMT individually after starting the polypill). To mitigate this risk, we will ask participants to bring in all of their pill bottles to each study visit. When participants start the polypill, we will collect all individual GDMT pill bottles. When participants start the individual pill regimen, we will collect all remaining doses of the polypill. Individual pill bottles that are not expired can be returned to the participant at the end of the study period, if requested and if not expired. Identification and birth date will be confirmed prior to returning a participant's medications.
- Risk of missing multiple medications as a result of the polypill intervention: Our hypothesis is that the polypill will improve adherence; however, it may worsen adherence for some patients. When a patient misses a dose of a polypill, it would be equivalent to missing doses of several of their medications (rather than just one). To mitigate this risk, we will assess patients' adherence at each follow-up visit. We will ask patients to contact the study team sooner if they are having difficulty with the medication (e.g. not taking the polypill due to pill size), at which point we would determine the polypill to be intolerable for that patient, terminate the intervention, and resume all their medications as individual tablets.
- Risk of discomfort from pill size: The polypill will be larger than the individual component tablets, which could cause discomfort for some participants. We will show participants the projected polypill capsule size at time of study intake.
- Specific risks related to observation of pharmacists: Direct observation of pharmacy technicians for the purposes of measuring feasibility metrics may cause some discomfort for those being directly observed, or may cause distraction which could impact their work. To mitigate this risk, we will ask participants' consent to be observed and will minimize interaction with participants while they are working. A pharmacist will review the work by pharmacy technicians as part of their standard safety procedures. Furthermore, there could be privacy concerns if the study team sees the names or medications of individuals who are not part of the study. We will discuss this risk with the pharmacists, and arrive at a strategy to minimize breach of confidentiality for patients who are not part of the study.
- Phlebotomy: Blood draws at follow-up visits could be associated with pain, bruising, or hematoma formation. Blood draws will be limited to under 10cc to minimize risk to participants from phlebotomy.

- Breach of confidentiality: To minimize the risk of breach of confidentiality, all study staff will have completed CITI Human Subjects Protection Training and comply with privacy and data protection measures approved by the UCSF IRB. All appropriate measures will be taken for the protection of personally-identifiable health information (PHI), including de-identification of all patient data objects.

Exit interviews:
-Discomfort: For healthcare professionals (ZSFG clinicians or Daniel's Pharmacy staff), some questions about their opinions on the study intervention may cause discomfort. For patients, some questions about personal health practices or medication-taking adherence may make patients feel uncomfortable. At the start of each interview, participants will be advised that they may decline to answer any questions.
-Breach of confidentiality: as with other qualitative research, there is a risk of interviews being overheard. As such, semi-structured interviews will be conducted in private rooms. Some interviews may be conducted over telephone or secure video conferencing.

14.3

MINIMIZING RISKS: Describe the steps you have taken to minimize the risks/discomforts to subjects. Examples include:

- **designing the study to make use of procedures involving less risk when appropriate**
- **minimizing study procedures by taking advantage of clinical procedures conducted on the study participants**
- **mitigating risks by planning special monitoring or conducting supportive interventions for the study**
- **having a plan for evaluation and possible referral of subjects who report suicidal ideation**

1. Informed Consent
Trained study investigators or clinical research coordinators will in-person informed consent discussions with each participant. The research staff will ensure that all questions have been addressed and the potential participant can confirm verbal understanding of the study's purpose, intervention, basic procedures, and risk, as well as expresses confirmation that participation in the study is voluntary. If the patient chooses to participate, they will sign the consent form and will be given a signed copy to keep, along with the HIPAA form and UCSF Subject Bill of Rights.

Participants may stop the study at any time if they feel uncomfortable or do not wish to disclose any requested information. If participants decide to withdraw from the study, any information collected up to that point will be retained unless the participant requests the data be destroyed. We will not identify participants in reports to minimize risks associated with disclosure of their responses. Any alarming health care concerns expressed by the participants in the in-depth interviews will be referred to their individual healthcare provider after obtaining permission from the participant.

2. Standardized Protections Against Risk
Records for all subjects will be handled as confidentially as possible. Patient records will be coded and maintained in a locked office, and the research team will maintain copies of the signed consent forms. All digital records will be stored on password-protected, encrypted servers. Biologic specimens and clinical data will be linked to unique subject IDs, and not to any identifying patient information.

3. Protection in the Event of Adverse Effects of Study Procedures
Patients will be monitored for adverse events throughout the study. The study will be conducted at ZSFG clinics, where there will be clinical staff available in case of any unanticipated severe adverse events.

14.4 RESOURCES: Describe the resources in place to conduct this study in a way that assures protection of the rights and welfare of participants: These resources typically include appropriately trained and qualified personnel (in terms availability, number, expertise and experience), funding, space, equipment, and time to devote to study activities. Depending on the nature of the research study, investigators should consider the proximity or availability of critical resources that may be essential to the safety and welfare of participants, such as

- **the proximity of an emergency facility for care of participant injury**
- **availability of psychological support after participation**
- **resources for participant communication, such as language translation services**

Staff:
The study team will include several attending cardiologists, including an advanced heart failure specialist. All of the study team will be appropriately trained and qualified for conduct of clinical research.

Location:
Study follow-up visits will be conducted at ZSFG clinics, in close proximity to emergency response personnel in case of participant injury. Participants will be provided with a study contact phone number, as well as strict precautions to call 9-1-1 in case of a serious adverse event related to their medication.

Professional pharmacy services:
Our pharmacy partner will be Daniel's Pharmacy, which is certified community pharmacy with extensive experience with multi-dose packaging, including blister packs; MediSets; and over-encapsulation.

Funding:
This study will be funded by a UCSF CAPS-HIV Innovative Grant.

14.5 * BENEFITS: (REQUIRED) Note: These are the benefits that the IRB will consider during their review. They are not necessarily appropriate to include in the consent form.

Possible immediate and/or direct benefits to participants and society at large (check all that apply):

- [x] Positive health outcome (e.g. improvement of condition, relief of pain, increased mobility, etc.)
- [x] Closer follow-up than standard care may lead to improved outcomes or patient engagement
- [ ] Health and lifestyle changes may occur as a result of participation
- [ ] Knowledge may be gained about their health and health conditions
- [x] Feeling of contribution to knowledge in the health or social sciences field
- [ ] The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children
- [ ] Other benefit (describe below)
- [ ] None

14.6 RISK TO BENEFIT RATIO: Explain why the risks to subjects are reasonable in relation to anticipated benefits, if any, to the participant or society:

The primary benefit of this study is the knowledge of contributing to research, which could in the future lead to new delivery systems for heart failure medications. Secondly, participants will be seen more frequently than standard care, which could have potential health benefits. Finally, if the polypill is an effective adherence intervention, it may positively impact participants' adherence to GDMT for the duration of the trial period. Participants will continue to pay standard medication copays if applicable, unless the copay is solely attributable to participation in the trial (for example, if they have a copay as a result of switching from metoprolol to bisoprolol for the purposes of the polypill intervention).

We believe that the risks to participants are low, and will be further mitigated by close clinical follow-up for the duration of the pilot trial. Patients who choose to participate in the study will be contributing to research that we hope will improve access to cardiovascular therapies in the future.

15.0 Data and Safety Monitoring Plan

15.1 * DATA AND SAFETY MONITORING PLAN (DSMP): (REQUIRED) Provide a summary of the DSMP:

All greater than minimal risk studies are required to provide a plan. Lack of an adequate plan is one of the most common reasons why IRB approval is delayed.

Instructions:

Describe the plan for monitoring data quality and participant safety. Key areas that should be included in the plan are:

- An explanation of the plan to monitor data collection, study progress, and safety
- A description of who will perform the monitoring and at what frequency (e.g., the PI only, a contract research organization, a Data and Safety Monitoring Board or Data Monitoring Committee, etc.)
- The type of data and events that will be reviewed (e.g., adverse events, breaches of confidentiality, unanticipated problems involving risk to participants or others, unblinded efficacy data, etc.)
- Procedures and timeline for communicating monitoring results to the UCSF IRB, the study sponsor, and other appropriate entities

As appropriate:

- A plan for conducting and reporting interim analysis
- Clearly defined stopping rules
- Clearly defined rules for withdrawing participants from study interventions

Data and safety monitoring will be performed by the research team. At weekly research team meetings, any data events (including suspected breaches of confidentiality, unanticipated risks to participants or others, or other adverse events) will be reviewed by the study team. Any unforeseen data or safety events will be reported to the UCSF CHR within 7 days.

Specifically, the study team will conduct internal interim safety analyses at 4 and 8 weeks. At these meetings, we will review safety data including preliminary impact on adherence (positive or negative); documented episodes of medication-related adverse effects; and any ER presentation or hospital admission of study participants. Any adverse events will be promptly reported to the UCSF CHR and the study sponsor (UCSF CAPS). If adverse events are possibly attributable to study procedures, potential outcomes could include: continue the study with increased monitoring schedule, stop the trial for a single participant or group of participants, or stop the study altogether. Precise stopping rules will be finalized after formative interviews with cardiologists and patients in qualitative Aim 1.

Additional information on the plan for confidential data collection and storage is outlined below.

Data Monitoring Plan to Ensure the Safety of Participants:
Recorded interviews will be stored as audio files on a password-protected, secure online server. Any alarming health care concerns expressed by the participants in the in-depth interviews will be referred to their individual healthcare provider after obtaining permission from the participant. Electronic surveys will be administered via REDCap and the link between identifiers and data will be destroyed after the completion of the study.

Data Banking:
Data will be retained for the duration of the study, and access will be limited to the research team outlined in this protocol. Data will be stored at UCSF within a secure, encrypted, password-protected REDCap database server. Alter completion of the study, the link between identifiers and data will be destroyed.

Data Sharing:
Any data shared with other institutions for ongoing research activities will be de-identified and password protected. De-identified data intended for research purposes may be shared upon written request to the Principal Investigators.

Provisions to Protect the Privacy and Confidentiality of Participants and the Research Data:
Participants may choose to withdraw from the study at any point. Along with explicit outlining of

the study procedures, this ability of participants to withdraw will be clearly stated to each participant at the start of each interview.

Audio Recording:
The key informant in-depth interviews will be audio recorded with the participant's consent. Prior to the start of the recording, participants will be asked to provide a pseudonym or first name. Recording can be paused or stopped, if requested by participants, at any time.

Audio recordings will be copied to secure, encrypted, password-protected servers at UCSF. After audio transcription, all recordings on encrypted devices will be destroyed. De-identified transcripts and research records will be kept on secure, encrypted, password-protected servers at UCSF for a minimum of 7 years after the end of the study.

15.2 * DATA AND SAFETY MONITORING BOARD (DSMB): (REQUIRED) Will a Data and Safety Monitoring Board (DSMB) be established:

- ○ Yes
- ◉ No

Guidelines

A Data and Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC) is a formal, independent committee that is specifically established to conduct interim monitoring, oversight and analysis of study information and data to assure the continuing safety, efficacy, appropriateness, relevance, and integrity of the study.

The UCSF IRB reserves the right to request a DSMB/DMC for any study. However, the following are factors that the IRB will consider when making this determination:

- There is a significant likelihood of a serious adverse event to subjects
- The study is conducted at multiple sites and the level of risk is greater than minimal
- The study generates data that are blinded or randomized
- The study involves a large number of patients randomized to one of two or more interventions
- A study for which the performance of an interim analysis is crucial for the protection of the subjects
- First use in humans
- First use in children
- The study involves gene therapy, stem cell therapy, or other novel interventions for which long-term outcome data are not known or available

16.0 Confidentiality, Privacy, and Data Security

16.1 * PROTECTING PRIVACY: Indicate how subject privacy will be protected: (REQUIRED)

- ☑ Conduct conversations about the research in a private room
- ☑ Ask the subject how they wish to be communicated with – what phone numbers can be called, can messages be left, can they receive mail about the study at home, etc.
- ☑ Take special measures to ensure that data collected about sensitive issues do not get added to their medical records or shared with others without the subject's permission
- ☐ Other methods (describe below)

16.2 * SENSITIVE DATA: Do any of the instruments ask about illegal or stigmatized behavior: (REQUIRED)

○ Yes ◉ No

16.3 * SIGNIFICANT CONSEQUENCES OF A LOSS OF PRIVACY OR CONFIDENTIALITY: Could a breach of privacy or confidentiality result in any significant consequences to participants, such as criminal or civil liability, loss of state or federal benefits, or be damaging to the participant's financial standing, employability, or reputation: (REQUIRED)

○ Yes ◉ No

16.4 EXTRA CONFIDENTIALITY MEASURES: Explain any extra steps that will be taken to assure confidentiality and protect identifiable information from improper use and disclosure, if any:

Study follow-up visits will be conducted on-site at ZSFG or by secure Zoom or telephone in private, quiet rooms. Interviews will be conducted by HIPAA-compliant Zoom, telephone, or in person in a quiet, private room in an affiliated ZSFG cardiology clinic. Recorded interviews will be stored as audio files on a password-protected, secure online server. Any alarming health care concerns expressed by the participants in the in-depth interviews will be referred to their individual healthcare provider after obtaining permission from the participant. Electronic surveys will be administered via REDCap and the link between identifiers and data will be destroyed after the completion of the study.

16.5 * REPORTABILITY: Do you anticipate that this study may collect information that State or Federal law requires to be reported to other officials, such as elder abuse, child abuse, or threat to self or others, or HIV status and other reportable conditions: (REQUIRED)

○ Yes ◉ No

16.6 * CERTIFICATE OF CONFIDENTIALITY: Will this study obtain a Certificate of Confidentiality: (REQUIRED)

○ Yes ◉ No

16.7 * SHARING OF RESEARCH RESULTS: Will there be any sharing of EXPERIMENTAL research test results with subjects or their care providers: (REQUIRED)

○ Yes ◉ No

16.9 * HIPAA APPLICABILITY: Study data will be: (REQUIRED)

- ☑ Derived from a medical record (e.g. APeX, OnCore, etc. Identify source below)
- ☑ Added to the hospital or clinical medical record
- ☑ Created or collected as part of health care
- ☑ Used to make health care decisions
- ☑ Obtained from the subject, including interviews, questionnaires
- ☐ Obtained ONLY from a foreign country or countries
- ☐ Obtained ONLY from records open to the public
- ☐ Obtained from existing research records
- ☐ None of the above
- ☐ Derived from the Integrated Data Repository (IDR) or The Health Record Data Service (THREDS) at ZSFG

In addition to signing a consent form, each subject will have to sign the UCSF Participant Authorization for Release of PHI for Research (HIPAA Form). Upload the HIPAA Form in the Other Study

Documents section of the Initial Review Submission Packet Form. Failure to have patients sign the HIPAA Authorization is one of the most common findings from QIU Routine Site Visits.

Guidance about HIPAA requirements and other HIPAA-related forms are available online on the IRB's HIPAA page.

If derived from a medical record, identify source (UCSF Health APeX, SFDPH Epic, VA CPRS, etc.):

SFDPH Epic

16.10 * GDPR APPLICABILITY: Answer the following questions to determine if this study is subject to additional data privacy regulations under the General Data Protection Regulation (GDPR and/or UK GDPR): (REQUIRED)

* Is the study targeting or recruiting **European Economic Area (EEA)** or United Kingdom (U.K.) participants, or collecting and using the personal data of participants located in the EEA or the U.K.: **(REQUIRED)**

NOTE: If this study is being carried out online and may recruit people living in the EEA zone or the U.K., you should check 'Yes.'

- ○ Yes
- ◉ No

* Is the study receiving data from a site that is collecting data from individuals located in the EEA or U.K. nations: **(REQUIRED)**

- ○ Yes
- ◉ No

16.11 * IDENTIFIERS: Will any of the following identifiers be collected and included in the research records, even temporarily: (REQUIRED)

- ☑ Names
- ☑ Dates
- ☐ Postal addresses (if only requesting/receiving zip codes check Yes to the Zip Code question below instead of checking this box)
- ☑ Phone numbers
- ☐ Fax numbers
- ☐ Email addresses
- ☐ Social Security Numbers*
- ☑ Medical record numbers
- ☐ Health plan numbers
- ☐ Account numbers
- ☐ License or certificate numbers
- ☐ Vehicle ID numbers
- ☐ Device identifiers or serial numbers
- ☐ Web URLs
- ☐ IP address numbers
- ☐ Biometric identifiers
- ☐ Facial photos or other identifiable images
- ☐ Any other unique identifier
- ☐ None

* Could study records include *ANY* photos or images (even 'unidentifiable' ones): **(REQUIRED)**

○ Yes ◉ No

16.13 * PATIENT MEDICAL RECORDS: Will health information or other clinical data be accessed from UCSF Health, Benioff Children's Hospital Oakland, or Zuckerberg San Francisco General (ZSFG): (REQUIRED)

◉ Yes ○ No

16.16 * HIPAA - PERMISSION TO ACCESS SENSITIVE DATA: Does the research require access to any of the following types of health information from the medical record: (check all that apply) (REQUIRED)

- ☐ Drug or alcohol abuse, diagnosis or treatment
- ☑ HIV/AIDS testing information
- ☐ Genetic testing information
- ☐ Mental health diagnosis or treatment
- ☐ None of the above

Important note: Ensure that participants initial the corresponding line(s) in Section C of the HIPAA authorization form during the consent process.

16.20 * DATA COLLECTION AND STORAGE: (check all that apply): (REQUIRED)

Collection methods:

- ☐ Electronic case report form systems (eCRFs), such as OnCore or sponsor-provided clinical trial management portal
- ☑ UCSF ITS approved Web-based online survey tools: Qualtrics or RedCap
- ☐ Other web-based online surveys or computer-assisted interview tool
- ☐ Mobile applications (mobile or tablet-based)
- ☐ Text Messaging
- ☐ Wearable devices
- ☑ Audio/video recordings
- ☐ Photographs
- ☐ Paper-based (surveys, logs, diaries, etc.)
- ☐ Other:

* What online survey or computer assisted interview tool will you use: **(REQUIRED)**

- ☐ Qualtrics (Recommended)
- ☑ RedCAP (Recommended)
- ☐ Survey Monkey (NOT recommended and may require UCSF ITS Security review)
- ☐ Other

* Data will be collected/stored in systems owned by (check all that apply): **(REQUIRED)**

- ☐ Study sponsor
- ☑ UCSF data center (including OnCore, RedCap, Qualtrics, and MyResearch)
- ☑ UCSF encrypted server, workstation, or laptop residing outside of UCSF data center
- ☐ Personal devices, such as laptops or tablets that are not owned or managed by UCSF
- ☐ San Francisco VA Health Care System (SFVAHCS)
- ☐ Zuckerberg San Francisco General Hospital

- [ ] Benioff Children's Hospital Oakland
- [ ] Langley Porter Psychiatric Institution
- [ ] Other UCSF affiliate clinic or location (specify below)
- [ ] Cloud vendor such as Amazon Web Services (AWS), Salesforce, etc. (specify below)
- [x] Other academic institution
- [ ] 3rd party vendor (business entity)
- [ ] Other (explain below)

16.21 * ADDITION OF RECORDS TO A REGISTRY: Will patient records reviewed under this approval be added to a research database, repository, or registry (either already existing or established under this protocol): (REQUIRED)

- ( ) Yes (•) No

16.22 * DATA SHARING: During the lifecycle of data collection, transmission, and storage, will identifiable information be shared with or be accessible to anyone outside of UCSF: (REQUIRED)

- (•) Yes ( ) No

* Who will have access to the data: **(REQUIRED)**

- [ ] Collaborators listed in the study application
- [ ] NIH or other shared data repository
- [ ] Sponsors
- [ ] FDA
- [x] Other 3rd party (such as vendors/contractors)

IMPORTANT: The IRB now recommends that all consent forms include a provision for sharing of de-identified/coded data to permit re-use of data for secondary research purposes. This doesn't apply if you've been granted a waiver of consent for this study.

* Provide the details of whom the data will be shared with and what types of information and identifiers will be shared: **(REQUIRED)**

Our pharmacist partner, Daniel's Pharmacy, will receive prescriptions for heart failure medications for study participants, which will include the patients' name, birth date and medical record number. The pharmacy will provide the medications as well as the packaging services, but will be in a contracting role and is not engaged in human subjects research.

Our research collaborators at Washington University in St. Louis will assist with review of deidentified data for the purposes of analysis and manuscript preparation. This may include deidentified transcripts from exit interviews, which our Wash U collaborators may help to code and analyze. No identifiable patient information will be stored on Wash U servers, nor accessed by investigators outside of UCSF.

16.23 * DATA SHARING METHODS: How will data be securely shared with the 3rd party: (REQUIRED)

- [ ] Collaborators will access data in MyResearch
- [ ] Collaborators will access data in REDCap
- [ ] Collaborators will be sponsored as an affiliate and be treated as an UCSF user (includes using UCSF Box)
- [ ] UCSF Secure Email will be used to share data
- [ ] Collaborator's or Sponsor's system will be used (specify below)
- [x] Other method (describe below)

Please provide details about how the data will be shared:

Daniel's Pharmacy will receive electronic prescriptions for heart failure medications via SFDPH Epic, as is done in non-research settings. For study participants, the "Note to Pharmacy" will include instructions on co-packaging the pills into a heart failure polypill. The study team will also communicate frequently with Daniel's Pharmacy staff by telephone or secure email to track prescription fulfillment and delivery to study participants.

17.0 Financial Considerations

17.1 * PAYMENT: Will subjects be paid for participation or receive any other kind of compensation: (REQUIRED)

(•) Yes ( ) No

17.2 * REIMBURSEMENT: Will participants be reimbursed for expenses related to study participation: (REQUIRED)

(•) Yes ( ) No

Describe the reimbursement that will be available to participants:

Bus tokens, parking vouchers, or other transportation vouchers will be provided as needed.

17.3 * PAYMENT/REIMBURSEMENT METHODS: Participant payment or compensation methods (check all that apply): (REQUIRED)

Payments will be (check all that apply):

- [ ] Cash
- [ ] Check
- [x] Gift card
- [ ] Debit card
- [ ] UCSF Research Subject Payment Card
- [ ] Reimbursement for parking and other expenses
- [ ] Other:

17.4 * PAYMENT SCHEDULE: Describe the schedule and amounts of payments, including the total subjects can receive for completing the study: (REQUIRED)

- **If there are multiple visits over time, explain how payments will be prorated for partial completion**
- **If deviating from recommendations in Subject Payment Guidelines, include specific justification below**

Participants will receive a $10 gift certificate for each visit, with an additional $30 if they bring in their pill bottles and an additional $10 for any blood draws that are needed for the purposes of the study. The gift card will be provided to participants at the time of each visit or interview.

We will also offer $20 gift cards to patients and ZSFG clinicians for participation in a 30-60 minute exit interview. Daniel's Pharmacy staff will be paid for their time for exit interviews, as with their time spent manufacturing polypills, according to an hourly fee schedule.

The maximum compensation per participant will be approximately $260 ($10 each for up to 6 trips to the hospital - including study and lab visits, $10 each for up to 6 lab draws, $30 each for bringing their pill bottles to the 4 study visits, and $20 for an exit interview).

17.5 * COSTS TO SUBJECTS: Will subjects or their insurance be charged for any study activities:

(REQUIRED)

◉ Yes ○ No

Describe the costs that may be incurred by subjects or 3rd party payers as a result of participation:

- Explain why it is appropriate to charge those costs to the subjects
- If this is a therapeutic study, compare subjects' costs to the charges that would typically be associated with receiving care off-study (e.g. is it more expensive to participate in this study than to receive care off-study?)

There will be no cost to subjects, other than time provided to participate in the study. We will recruit participants on-site at ZSFG in order to avoid additional travel costs for patients; we will also provide bus tokens or travel vouchers if needed.

Since the polypill is primarily a medication packaging intervention (like a bubble pack or MediSet), participants' heart failure therapies will continue to be charged to their insurance, and they may be charged medication copays if applicable (although most patients enrolled in SF Health Plan or MediCal have zero copays for their heart failure medications). The total charges should be the same whether they are in the control arm (medications dispensed individually) or the polypill arm (medications packaged into a polypill at the pharmacy).

Patients who are not already on guideline-directed heart failure therapies may be started on new medications at the start of the study, which could incur additional copays for the patient. Since study clinicians are all part of the ZSFG cardiology department, and since all the medications are standard guideline-directed therapies, we do not anticipate that there will be any differences in insurance coverage of medications that are prescribed during study visits vs. standard care visits. If there are additional costs that are specific to participation in the study (for example, needing to refill a patient's medications early because they enrolled in our polypill trial), those costs will be covered by the study team. Otherwise, standard copays will be paid by patients as usual.

As with a bubble pack, the polypill will require that some medications be picked up together on the same day (rather than filling individual medications on different days), which could result in a larger financial outlay at one time for patients with medication copays. As with a bubble pack or blister pack, dose adjustments for any component of the polypill will need to be implemented with the next month's polypill packaging. For time-sensitive changes, the remaining supply of polypills will need to be repackaged or replaced by the pharmacy. Compared to standard care with a bubble pack, we do not anticipate that the trial will significantly impact pharmacy costs for patients or payors.

18.0 Other Approvals and Registrations

18.1 * ADMINISTRATION OF RECOMBINANT DNA: Does this study involve administration of vaccines produced using recombinant DNA technologies to human subjects? (REQUIRED)

○ Yes ◉ No

18.2 * HUMAN GENE THERAPY: Does this study involve human gene therapy (also called "Human Gene Transfer": (REQUIRED)

○ Yes ◉ No

18.4 OTHER APPROVALS: Indicate if this study involves other regulated materials and requires approval and/or authorization from the following regulatory committees:

☐ Institutional Biological Safety Committee (IBC)

Specify BUA #:

☐ Institutional Animal Care and Use Committee (IACUC)

Specify IACUC #:

☐ Controlled Substances

19.0 Qualifications of Key Study Personnel and Affiliated Personnel

NEW: January 2019 - Affiliated personnel who do not need access to iRIS no longer need to get a UCSF ID. Instead, add them below in the Affiliated Personnel table below.

19.1 Qualifications of Key Study Personnel:

Instructions:

For UCSF Key Study Personnel (KSP)* listed in **Section 3.0,** select the KSP from the drop down list and add a description of their study responsibilities, qualifications and training. In study responsibilities, identify every individual who will be involved in the consent process. Under qualifications, please include:

- Academic Title
- Institutional Affiliation (UCSF, ZSFG, SFVAHCS, etc.)
- Department
- Certifications

NOTE: This information is required and your application will be considered incomplete without it. If this study involves invasive or risky procedures, or procedures requiring special training or certification, please identify who will be conducting these procedures and provide details about their qualifications and training. Click the orange question mark for more information and examples.

Training Requirements:
The IRB requires that all Key Study Personnel complete Human Subjects Protection Training through **CITI** prior to approval of a new study, or a modification in which KSP are being added. More information on the CITI training requirement can be found on our **website.**

* **Definition of Key Study Personnel and CITI Training Requirements (Nov, 2015):** UCSF Key Study Personnel include the Principal Investigator, other investigators and research personnel who are directly involved in conducting research with study participants or who are directly involved in using study participants' identifiable private information during the course of the research. Key Personnel also include faculty mentors /advisors who provide direct oversight to Postdoctoral Fellows, Residents and Clinical Fellows serving as PI on the IRB application.

KSP Name	Description of Study Responsibilities - Briefly describe what will each person be doing on the study. If there are procedures requiring special expertise or certification, identify who will be carrying these out. Also identify who will be obtaining informed consent.	Qualifications, Licensure, and Training
Dejong, Colette C	Principal investigator	Dr. Colette DeJong is a cardiology fellow and researcher at the University of California, San Francisco, with research experience in disparities in cardiovascular care.
Dr. Hsue, Priscilla MD, MD	Senior investigator, faculty mentor	Dr. Priscilla Hsue is the Maurice Eliaser Jr. Distinguished Professor of Medicine at the University of California, San Francisco, Chief of Cardiology at Zuckerberg San Francisco General Hospital, and Co-Director of the UCSF Center for Vascular Excellence. She is an international expert on the relation between inflammation, immune dysfunction, and cardiovascular disease. She has extensive experience conducting Phase II and Phase III clinical trials of anti-inflammatory, immunomodulatory, and lipid lowering therapies for HIV, rheumatoid arthritis, atherosclerosis, and COVID-19.
Dr. Durstenfeld, Matthew S MD	Co-investigator	Dr. Matt Durstenfeld is a non-invasive general cardiologist and researcher with experience global cardiology, infectious-disease related cardiovascular disease, and disparities in cardiovascular care. He is an Assistant Professor of Medicine at the University of California, San Francisco.
	Co-investigator,	Dr. Wayne Steward is a research psychologist with expertise in the

Dr. Steward, Wayne PhD	qualitative methods expert	development of innovative care models for people with HIV.
Dr. Riley, Elise PhD	Co-investigator, epidemiologist	Dr. Elise Riley is an infectious disease epidemiologist and professor of medicine at UCSF, has extensive experience researching the combined effects of HIV, substance use, housing instability, and medical comorbidities on cardiovascular health.
Dr. Hickey, Matthew D MD	Co-investigator	Dr. Matt Hickey is a clinician and researcher based at Ward 86, with an interest in implementation science and novel approaches to expand access to care among PWH at ZSFG.
Dr. Zier, Lucas S MD	Co-investigator	Dr. Zier is an interventional cardiologist and researcher at ZSFG.
Schaffer, Veronica	Clinical research coordinator	Veronica Schaffer is a clinical research coordinator in Dr. Priscilla Hsue's group at ZSFG.

19.2 Affiliated Personnel:

Instructions:

This section is for personnel who are not listed in **Section 3.0: Grant Key Personnel Access to the Study** because their names were not found in the User Directory when both the iRIS Database and MyAccess directories were searched. Add any study personnel who fit ALL of the following criteria in the table below:

- They meet the definition of Key Study Personnel (see above), **and**
- They are associated with a UCSF-affiliated institution (e.g., SFVAHCS, Gladstone, Institute on Aging, Vitalant, NCIRE, SFDPH, or ZSFG), **and**
- They do not have a UCSF ID, **and**
- They do not need access to the study application and other study materials in iRIS.

Note: Attach a **CITI Certificate** for all persons listed below in the **Other Study Documents** section of the **Initial Review Submission Packet Form** after completing the **Study Application**.

Click the orange question mark icon to the right for more information on who to include and who not to include in this section.

Do not list personnel from outside sites/non-UCSF-affiliated institutions. Contacts for those sites (i.e. other institution, community-based site, foreign country, or Sovereign Native American nation) should be listed in the **Outside Sites** section of the application.

If there are no personnel on your study that meet the above criteria, leave this section blank.

Name	Institution	Telephone	E-mail	Role
Christina Wang	ZSFG	628-206-0261	christina.s.wang@sfdph.org	Other Investigator

Please describe the study responsibilities and qualifications of each affiliated person listed above:

Christina Wang, PharmD is an anticoagulation and cardiovascular pharmacist at ZSFG. She will be involved in the study as a co-investigator. As a DPH clinician, she will also be responsible for reviewing lists of potential participants that may be contacted for recruitment, in accordance with Research at SFDPH ZSFG Dean's Office protocol.

20.0 End of Study Application

End of Study Application Form

To continue working on the Study Application:
Click on the section you need to edit in the left-hand menu. Remember to save through the entire Study Application after making changes.

If you are done working on the Study Application:
Important: Before proceeding, please go back to Section 4.0 Initial Screening Questions and **Save and Continue** through the form to make sure all the relevant sections and questions have been included. If you've changed any answers since you started, the branching may have changed. Your application will be incomplete and it will have to be returned for corrections.

Once you are sure the form is complete, click **Save and Continue**. If this is a new study, you will automatically enter the **Initial Review Submission Packet Form**, where you can attach **consent forms** or other **study documents**. Review the **Initial Review Submission Checklist** for a list of required attachments.

Answer all questions and attach all required documents to speed up your approval.

The UCSF IRB welcomes feedback about the IRB Study Application Form. Please click the link to answer a **survey** about the application form.