Document:

Study Protocol and Statistical Analysis Plan

Study Title:

An Accessible, Scalable, Patient-facing mHealth Application for Self-care of Heart Failure in LMIC

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1. BACKGROUND

Heart failure (HF) is a non-communicable disease (NCD) that affects more than 38 million people globally.(1,2) In sub-Saharan Africa (SSA), HF is responsible for up to 7% of hospital admissions and a high premature mortality rate.(3,4) HF is a clinical syndrome with diverse causes, such as hypertension and rheumatic heart disease, that results in multiple debilitating symptoms. These symptoms can often be managed by patients themselves, when given the tools to engage in selfcare. Self-care is a World Health Organization-endorsed intervention for NCD with a strong evidence base and critical advantages in low-resource settings. It benefits both patients and health systems by shifting fundamental care tasks from providers to patients while empowering patients and enhancing well-being.(5) Self-care for HF includes behaviors such as controlling dietary intake of sodium and recognizing and treating symptoms such as shortness of breath. Despite its benefits, self-care for HF remains underutilized globally, especially in low- and middle-income countries (LMIC).(6) In Uganda, self-care is identified as one of the greatest unmet needs among patients with HF.(7) mHealth offers a promising platform to close this performance gap in LMIC, by leveraging the widespread penetration of mobile phones to offer individualized self-care tools such as education, healthy lifestyle messaging, and decision support directly to patients with HF.(8-10)

In 2016, our multi-national team began collaborating to adapt Medly, a smartphone-based mHealth application for self-care of HF, developed and tested in Canada, to the setting of Uganda. Medly was shown to improve self-care and health-related quality of life (HRQoL) in HF by generating personalized self-care instructions based on patient-entered symptoms and vital signs transmitted by telemonitoring devices. Through formative work among patients with HF and providers at the Uganda Heart Institute (UHI) in Kampala, we learned that patients commonly have significant HF symptoms but do not routinely engage in self-care. This is due to lack of knowledge about self-care options and actions to take in response to symptoms. Despite this, both providers and patients were optimistic about a mHealth application that could improve self-care in HF.

Our research team has designed Medly Uganda for low-cost feature phones using a simpler interface with an algorithm that generates self-care instructions based on patient-reported symptoms alone. We have based the app on the Unstructured Supplementary Service Data (USSD) platform, a universally available interface that enables users to navigate hierarchical menus and offers multiple advantages for mHealth, including enhanced security features, verifiable transactions, simple navigation, and real-time interaction. (11,12) Though the Short Messaging Service (SMS) platform has been more widely used in mHealth, Ugandans commonly use and trust USSD for secure Mobile Money transactions. Furthermore, we designed a simple, secure, webbased dashboard for clinicians to monitor safety alerts generated by the app based on patient symptom reporting. Finally, we embedded Medly Uganda within FamilyConnect (FC)`, a Ugandangovernment-endorsed, hybrid USSD-SMS platform with proven feasibility and user engagement that currently provides pregnant women with health education and self-care recommendations. No member of the research team stands to profit financially from the current project or future iterations of Medly Uganda.

2. AIMS

Self-care is an important, yet underutilized, intervention in the management of chronic conditions, especially for low-resource settings because it shifts fundamental care tasks from providers to patients while empowering patients and enhancing quality of life. In this project, we will study the implementation and preliminary clinical effectiveness of Medly Uganda, a patient-facing mobile health application designed to improve self-care among patients within heart failure. The multi-level engagement of stakeholders and the grounding in user-centered design principles will serve to enhance the feasibility and scalability of Medly Uganda.

AIM 1: Assess the implementation of Medly Uganda at the Uganda Heart Institute in Kampala, Uganda. We will use mixed methods to assess feasibility, acceptability, and adoption of the app and accompanying provider dashboard. Sources of data will include surveys and interviews with patient and clinician participants and app and dashboard usage data.

AIM 2: Assess the preliminary effectiveness of Medly Uganda on clinical outcomes. Our primary outcome is improvement in the Self-Care in Heart Failure Index, a widely used, evidencebased instrument which we will evaluate at 0,3, and 6 months. We will also assess changes in HRQoL using the brief EQ-5D tool as well as the 6-Minute Walk Test, left ventricular ejection fraction, and frequency of acute care visits at the same time points.

3. STUDY PROTOCOL

3.1. Study Setting

Uganda is a low-income country in East Africa with a population of 35 million and a rising burden of NCD. Resource allocation toward NCD has been poor and the capacity of public sector healthcare facilities to

address NCD, including HF, is low. The proposed project will be conducted at UHI, the highest level referral center for cardiac care in the country and the only public sector facility with robust HF services. UHI is located on the campus of Mulago National Referral Hospital in the capital city, Kampala. Its outpatient clinic serves 70-100 adult patients per day from throughout Uganda and neighboring countries and from across socioeconomic and demographic spectra. Clinical care is provided by 12 physicians, 6 fellows, and 18 nurses. The coordinating center for this project is the Uganda Initiative for Integrated Management of Non-Communicable Disease (UINCD), a research consortium co-directed by the co-Principal Investigators (PI) UINCD headquarters are located on Mulago campus, thereby allowing for ease of communication and collaboration between the clinical research site and the coordinating center.

In Uganda, in 2016, there were 22 million active mobile phone accounts and 340,000 land-lines, a ratio similar to other LMIC where mobile telephony became ubiquitous while circumventing land-line infrastructure. Cellular signals of the three main carriers are strong throughout the country. Given these features, Uganda has seen numerous mHealth pilot studies, many of which failed to progress beyond pilot stage due to lack of contextually appropriate design and testing and lack of engagement with key stakeholders. In response to this so-called "pilotitis", all mHealth projects are now required to exhibit genuine local ownership/co-ownership and collaboration with relevant government entities, which we demonstrate in the current proposal.

3.2. Study Design

This is a single-center prospective cohort study conducted at UHI. The study period is 6 months. Patient participants will have three study timepoints (Baseline, Month 3, and Month 6) while data will be collected from clinician participants only at Month 6.

3.3. Research Team and Collaboration Plan

As an expert in NCD healthcare delivery in Uganda with more than ten years of experience in developing research partnerships and strengthening local clinical, educational, and research capacity, Dr. Schwartz is well-positioned to lead the proposed grant alongside Dr. Ssinabulya, a Ugandan clinician researcher and expert in HF, hypertension, and empowerment of patients with cardiac disease. A transdisciplinary team of co-Investigators (co-I) with complementary expertise will support the PIs. These include Dr. Cafazzo (mHealth design and evaluation), Dr. Ross (HF self-care), Dr. Nalwadda (mixed methods NCD research), Professor Sewankambo (institutional leadership and research capacity strengthening), Dr. Lwabi (clinical leadership and cardiovascular medicine capacity strengthening), and Dr. Davis (mHealth and implementation science). Additionally, our MOH consultants will ensure that our research continues to leverage FC and align with MOH priorities.

Since 2016, the research team has conferred regularly over Skype, email, and in-person. Drs. Schwartz and Ssinabulya presented the current body of work at an international scientific conference in Uganda in 2018 (see Biosketches). As co-Directors of UINCD, they confer regularly regarding all aspects of UINCD's research and training agenda. Drs. Cafazzo and Ross have made site visits to UHI and UINCD. Over the three months prior to submission, the research team has met weekly. We will continue to employ these successful communication strategies for the duration of the grant period and will plan to meet in person once per grant year, concurrent with the annual mHealth-NCD Research and Training Symposia (see Research Capacity Strengthening Plan).

3.4. Procedures

Study procedures will be conducted by the Research Nurse (RN), unless otherwise noted. A Research Assistant (RA) with experience in qualitative data collection will conduct semi-structured interviews (SSI) and assist the RN with data collection. Quantitative data will be entered directly into a secure, UINCD tablet using Qualtrics software. Qualitative data will be audio recorded using a UINCD recording device. We will have samples of the two most common feature phones and

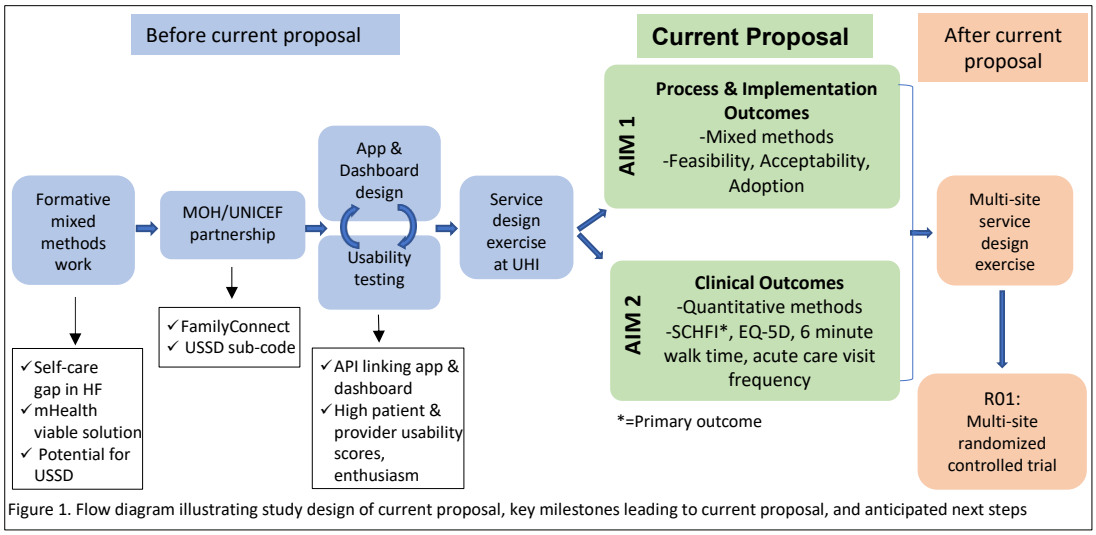

Figure 1. Flow diagram illustrating study design of current proposal, key milestones leading to current proposal, and anticipated next steps

smartphones onsite to allow participants who do not have a phone with them at this time to fully participate in on-site study procedures (registration and on-boarding). There are three study timepoints for patient participants: Baseline, Month 3, and Month 6. Study procedures include multiple widely used, validated clinical measurements: Self-Care in Heart Failure Index (SCHFI), EQ-5D, Six-Minute Walk Test (6MWT), and limited transthoracic echocardiogram for measurement of Left Ventricular Ejection Fraction (LVEF). Echocardiograms will be performed by a UHI cardiologist but interpreted en bloc and blinded at study conclusion to avoid interpretation bias. At Baseline, participants will complete informed consent, register in FC, orient to the app and message content, and conduct mock sessions until comfortable using the system, as determined by RN. We will also collect weight, vital signs, and a list of prescribed medicines. Urine pregnancy test will be done on women of childbearing age. SCHFI, EQ-5D, 6MWT, and LVEF will be completed. Clinician participants will be oriented to the app, dashboard, and expectations regarding their use by the RN. At Month 3, RN will review app activity with the participant and re-educate or re-orient them to the app, as needed. SCHFI, EQ-5D, 6MWT, and LVEF will be repeated. At Month 6, SCHFI, EQ-5D, 6MWT, and LVEF will be repeated. Participants will complete a feasibility survey and the RA will conduct an SSI using an interview guide (Appendix). Since the app is used on their personal phone, they will retain this device. Following the Month 6 visit, patient participants will be able to continue using Medly Uganda, however, depending upon the funding environment, may be responsible for associated USSD and SMS costs. Upon completion of Month 6 procedures by all active patient participants, clinician participants will complete a modified feasibility survey and the RA will conduct an SSI using a different interview guide.

Procedure	Comments
SCHFI	22-item instrument validated and used in LMIC settings. (6, 34)
EQ-5D	Generic, five-item HRQoL instrument validated and used in LMIC settings and for HF.(15, 60-64)
6MWT	Reproducible, submaximal exercise test to assess functional capacity in patients with cardiopulmonary conditions, including HF. Strong, independent predictor of morbidity and mortality in patients with HF. Measured in total distance walked independently in six minutes.(65-67)
LVEF	Widely recognized prognostic marker in HF and clinical outcome in HF self-care research. Percentage of blood ejected during systole.(68)

Table 1. Procedures include Self-Care in Heart Failure Index (SCHFI), EQ-5D, Six-Minute Walk Test (6MWT), and Left Ventricular Ejection Fraction (LVEF).

3.4. Intervention

Participants will be asked to initiate a USSD session by dialing the Medly Uganda sub-code and entering a unique PIN every Monday, Wednesday, and Friday morning for six months and whenever they experience concerning symptoms. If a participant has not done so by 11AM on the designated days, RapidPro will generate an SMS reminder. Each interactive USSD session will present a series of symptombased questions to the participant and be followed by a tailored SMS message. While USSD session content will not remain on the participant's phone, SMS' will. This allows participants to retain and review messages, thereby reinforcing educational content. There are four Status categories: Stable, Fluid Overload, Urgent, and Critical. If Stable, participants will be sent one of six encouraging and educational messages. If Fluid Overload, Urgent or Critical, patient participants will be sent a message that identifies the symptom and recommends an action and the on-duty nurse will be sent an accompanying alert. Urgent and Critical alerts will also be sent to the on-duty doctor (Algorithm- attached to HIC application). The nurse is expected to call the patient for Urgent and Critical alerts within 60 and 15 minutes, respectively. Nurse phone call interactions will be guided by a standard operating manual. One UHI nurse and one UHI doctor will be designated rotating 'on-duty' responsibility to monitor clinician alerts and the dashboard seven days a week. The doctor will be available to provide clinical supervision to the nurse as needed and they will have a daily in-person or by-phone huddle around 4PM to review the prior 24 hours system activity. Drs.Ssinabulya or Lwabi will be available at all times to provide an additional layer of technical and clinical backup to the designated clinicians as needed.

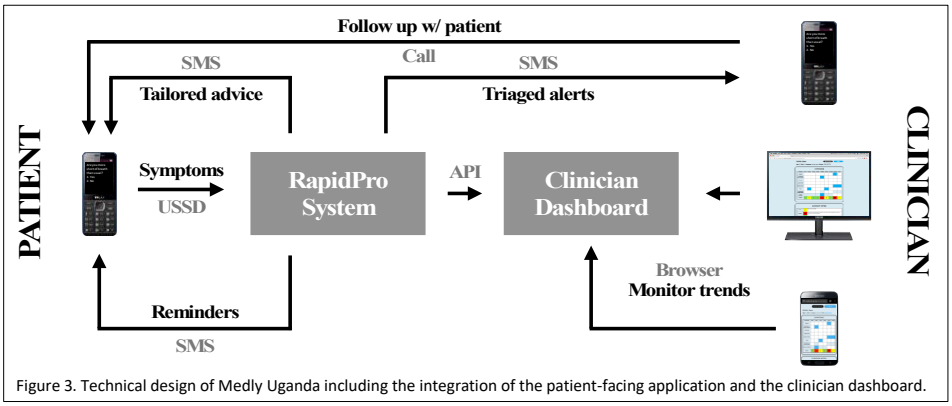

Figure 3. Technical design of Medly Uganda including the integration of the patient-facing application and the clinician dashboard.

Clinicians will access the dashboard by smartphone or computer using a unique username and password and entering the patient participant's phone number. The dashboard then presents a screen that includes basic demographic information, baseline clinical information from study entry. The screen also includes a color-coded matrix that graphically displays how the patient answered each question and the assigned Status from the current

and every prior USSD session. These are populated with data from RapidPro via API. An accompanying screen then allows the clinician to briefly summarize the content of their phone call and visualize all prior call entries.

Both app and dashboard contain security features approved by appropriate local stakeholders. As with mobile money, app access requires a valid SIM card associated with the registered user as well as a PIN. Dashboard access requires a username and password stored in non-human-readable form as generated by the bcrypt JavaScript library in the dashboard's PostgreSQL database.

3.4. Inclusion/Exclusion Criteria:

We will use consecutive sampling to identify potential patient participants. Based on UHI patient volume and demographics, we anticipate an equal distribution of urban- and rural-dwellers and 60:40 female:male ratio. For the clinician sample, we will seek to enroll all clinicians who meet inclusion/exclusion criteria (n=5 nurses; 5 doctors).

Patient inclusion criteria include: 1. UHI patient presenting for routine or urgent outpatient visit; 2. Currently living in Uganda and not planning to travel abroad for six months; 3. Age >=18 years; 4. Symptomatic (New York Heart Association Class II, III, or IV) HF regardless of LVEF; 5. Access to a mobile phone; 6. Basic reading skills in English, Luganda, and/or Runyankole.

Patient exclusion criteria include: 1. Life expectancy < six months; 2. Active medical condition requiring hospitalization, such as cardiac ischemia (acute electrocardiographic changes and/or positive biomarkers, if available), syncope, or significant fluid overload; 3. Pregnancy; 4. Inability to provide informed consent. *Clinician inclusion criteria* include: 1. UHI staff doctor or nurse; 2. Anticipated assignment to Medly Uganda duties at least once during the study period.

Clinician exclusion criteria includes unwillingness to provide informed consent.

4. STATISTICAL ANALYSIS

4.1. Sample Size:

Sample size calculation is based on published experience with SCHFI.(68) Given a sample size of 54 patients, we can detect a mean improvement of 10 points in SCHFI (primary outcome) at six months, assuming a standard deviation of 25 for the change of score (which gives effect size of 0.4), 2-sided type I error of 0.05, and power of 0.90. Allowing for a loss of 25% during the study, the *target sample size will be 72 patients*.

4.2. Statistical Methods for Aim 1:

This Aim focuses on a comprehensive evaluation of implementation and process outcomes for Medly Uganda at UHI. Quantitative data sources include an adapted feasibility survey exploring domains such as Acceptability and Practicality (Table 2) and app and dashboard usage data (Table 3). Qualitative data sources include SSI and dashboard content analysis (Table 2).

For *quantitative data*, descriptive statistics will be generated to characterize the feasibility, acceptability, and adoption of the app and dashboard. Mean (median) and standard deviation (range) for continuous variables and counts and proportions for categorical variables will be reported. The normality assumption of the distribution will be checked. If the normality assumption holds, the paired t-test will be used to evaluate changes in outcomes at Months 3 and 6. Otherwise the Wilcoxon signed rank test will be performed. For the *qualitative data*, interviews will be transcribed by RAs. A coding team will code all transcripts using the constant comparative method and a thematic analysis will be done using Atlas.ti software. Merged integration will be used to synthesize quantitative and qualitative findings using the Technology

Feasibility Domain	Content Area	Data Source
Acceptability	**Patients**: usefulness, confidentiality, impact on self-care	SSI, survey
	Clinicians: patient safety, clinical utility	SSI, survey
Practicality	**Patients:** mobile phone access, intended future use of app	SSI, survey
	Clinicians: burden of alerts, impact on clinical workflow	SSI, content analysis, survey

Table 2. Feasibility domains of interest, content areas for each participant type, and data sources.

Tool	Metric	Data Source
App	Frequency of USSD sessions (initiated, completed, incomplete) Questions per USSD session Duration of USSD session Status level assigned Message sent System fidelity to decision tree algorithm	RapidPro/MOH server
Dashboard	Frequency of logins, by role Actions taken Content entered Duration of session	UHI server

Table 3. App and dashboard metrics of interest and data sources.

Acceptance Model for Resource Limited Settings (TAM-RLS), a recent adaptation of the widely used TAM. TAM-RLS was created as a framework for evaluating mobile health interventions developed for resource-limited settings.(13) Finally, a content analysis will be conducted of dashboard entries. Drs. Davis, Cafazzo, and Ross will jointly support the PIs on the implementation process. Drs. Ssinabulya and Lwabi will oversee the quantitative methodology while Drs. Schwartz and Nalwadda will oversee the qualitative methodology and integration.

4.3. Statistical Methods for Aim 2:

This aim focuses on the evaluation of multiple clinical outcomes of local relevance and interest, all widely used in HF outcomes research. SCHFI (v.6) assesses three self-care domains- Maintenance, Management, and Confidence-using Likert scales.(34) Each domain is scored independently and standardized to a score of 100. The recommended time interval between administration is 3 months or less. Our primary outcome is specifically change in the Management scale, as this addresses the behaviors most closely tied to our intervention: active patient decision-making to identify symptoms and take actions to minimize them. EQ-5D assesses five domains – Mobility, Self-care, Usual activities, pain/discomfort, and anxiety/depression- using Likert scales and overall health using a visual analog scale. 6MWT and LVEF are measured in meters and percentage, respectively. Frequency of acute care visits will be abstracted from UHI clinical records and recorded as number of unscheduled visits in six months. Drs. Schwartz and Ssinabulya will co-lead this Aim.

4.3. Potential Challenges and Alternative Approaches:

First, participant dropout may occur due comprehension or technical challenges using the app, accessing a stable mobile network, or loss of interest. We will conduct interim analyses of follow-up rates and data completeness and adjust enrollment upward if needed. UHI has a sufficiently large eligible patient population to allow for this. Second, it is plausible that the need to enter a PIN could dissuade app use. If this is a consistent concern in Month 3 RN reviews, we will consider removing it after consultation with partners. Third, technical challenges may arise with the app or dashboard. A UHI Information Technology Specialist, already identified, will work with GoodCitizen to address such issues. Fourth, the frequency of alerts and calls could promote clinician burnout. Dr. Lwabi will monitor this through monthly check-ins with staff. UHI has sufficient staff to allow us to increase the number of clinician participants should this occur.

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