Study Title: Accelerating Delivery of rheUmatic heart disease preventive iNterventions in Northern Uganda (ADUNU)

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This document is a protocol for a research project. This study will be conducted in compliance with all stipulation of this protocol, the conditions of the ethics committee approval, the Uganda Heart Institute Research Ethics Committee (UHIREC), the Ugandan National Council of Science and Technology, University of Washington and the Cincinnati Children's Hospital Medical Centre IRB.

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PROTOCOL SYNOPSIS

TITLE	Accelerating Delivery of rheUmatic heart disease preventive iNterventions in Uganda (ADUNU)
OBJECTIVES	To evaluate the feasibility, sustainability, and public health impact of a district-based program (ADUNU) for secondary prevention of RHD in Uganda
DESIGN	Multiple-methods, prospective pre-post evaluation of public health program
OUTCOMES	1. Proportion of persons with RHD reached by program 2. Proportion of persons with RHD a. Enrolled in care b. Retained in care at 12 months c. Adherent to secondary prevention over 12 months 3. Organizational- and provider-level adoption of program (multidimensional) 4. Organizational- and provider-level implementation (multidimensional) 5. Sustainment of outcomes #1-4 at 24 months 6. Cost-effectiveness of program
STUDY DURATION	Five years
INTERVENTIONS	ADUNU is a public health program that will be deployed by the ministry of health in partnership with the District Health Offices in two districts (Kitgum and Amuru) and overseen by the Technical and Quality Assurance (TAQA) Work Group. The program's core components will be (i) RHD testing (community- and facility-based echocardiographic screening of children and younger adults), and (ii) provision of registry-based secondary prophylaxis injections at local HCIIIs and HCIVs. All people who will be diagnosed with RHD will be enrolled in the RHD National Registry, which is kept on an online platform, the ACT-Registry which is being rolled out across Uganda as the default care management system for RHD patients.
NUMBER OF PARTICIPANTS	1. Document review on MOH screenings of >100,000 individuals 2. Secondary analysis of registry data from 1844 anticipated registrants across two districts 3. Multiple-methods implementation research among samples of registrants (n=36 to

	42, depending on sub-objective), and providers/facility administrators (n=21 to 50, depending on sub-objective)
POPULATION	1. Individuals aged 5-39 residing in Kitgum and Amuru 2. All providers at HCIIIs and HCIVs located in Kitgum and Amuru

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GLOSSARY OF ABBREVIATIONS

ACT	Active Community Case Management Tool
ADD-RHD	Active case Detection and Decentralized dynamic registry to Improve the uptake of Rheumatic Heart Disease secondary prevention
ADUNU	Accelerating Delivery of rheUmatic heart disease preventive iNterventions in Uganda
ARF	Acute rheumatic fever
BIA	Budget impact analysis
BPG	Benzathine penicillin G
CEA	Cost-effectiveness analysis
CFIR	Consolidated Framework for Implementation Research
DHO	District health office
MOH	Ministry of health
RE-AIM	Reach-Effectiveness-Adoption-Implementation-Maintenance
RHD	Rheumatic heart disease
TAQA	Technical and Quality Assurance Working Group

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1.0 INTRODUCTION AND BACKGROUND

Rheumatic heart disease (RHD) is the most common acquired heart disease among children and young adults in Uganda and worldwide. Continuous antibiotic prophylaxis ("secondary prevention") is a cornerstone of RHD care supported by robust evidence.[1] Secondary prevention involves giving people with RHD 3- to 4-weekly administration of injectable benzathine penicillin G (BPG) or daily oral penicillin, a medication that reduces the chance that RHD will worsen and lead to serious and potentially fatal complications.[2] People who are diagnosed with RHD and are allergic to Penicillin are instead given oral Erythromycin. Echocardiography is the most sensitive and specific approach for identifying undiagnosed RHD in community-based settings,[3,4] but image capture and interpretation require specialised expertise that is lacking in many countries, so it has not been scaled up in national noncommunicable diseases or child health programmes.

Registry-based care is the consensus approach to delivering secondary prevention injections, but it is not being implemented by ministries of health (MOHs) in the countries where it is needed.[5] For example, in Uganda, the Uganda Heart Institute's National RHD Registry had about 3500 participants enrolled as of June 2022, which is only about 0.6% of the estimated number of persons with RHD in Uganda (around 550,000 in 2015). Importantly, this registry was created primarily for research, not clinical practice, and has not yet been adopted by the national MOH or integrated with other public health information systems.

Implementing guideline based RHD care also requires reducing patient barriers to access to diagnosis and treatment. An analysis of participants in the national RHD registry demonstrated that retention in care was a major gap, with the strongest predictor of retention being distance from the referral hospital where secondary prevention was being provided.[6] This observation, combined with the fact that the registry only covers a small proportion of the Ugandan population (i.e., those seeking care at UHI or three regional referral hospitals that are currently partnering with UHI on research), suggests that we need organised efforts to find more individuals with RHD and get them onto secondary prevention, ideally at health facilities close to where they live.

2.0 PROBLEM STATEMENT AND JUSTIFICATION

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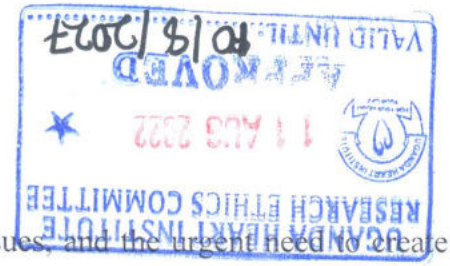

Considering these issues, and the urgent need to create new global knowledge on the implementation of effective RHD control programs that use echocardiography screening and registry-based delivery of secondary prevention, we propose ADUNU (Accelerating Delivery of rheUmatic heart disease preventive iNterventions in Uganda). ADUNU is intended to be a "demonstration project" to show how an RHD programme might work in the Ugandan context. ADUNU will define the district as the unit of intervention delivery (i.e., programme implementation through the DHOs, in partnership with the national MOH), and it will look at the effectiveness, feasibility, and affordability of an RHD programme in two districts (Kitgum and Amuru) that can serve as models for national scale-up in the years following this project. ADUNU is a direct response to the World Health Assembly RHD Resolution (passed in May 2018) that calls on Member States to prioritise RHD on their national health agendas[7] and addresses a request to UHI and the RHD Research Collaborative in Uganda (RRCU) from the Uganda MOH to assist in the development of an evidence-informed national RHD control strategy.

3.0 INNOVATION

Secondary prevention of RHD is an ideal target for implementation research: the core components of secondary prevention are effective and are supported by expert consensus, but we need scalable models that can improve RHD-related healthcare access and quality and can be financially sustained in Uganda and other African countries. To date, evidence on RHD control programs has come mostly from observational studies. The data are decades old and come from countries with relatively advanced healthcare systems, so there are essentially no useful contemporary data on ways to design effective RHD programs in limited-resource settings. The principal innovation of ADUNU is that it is the first attempt to systematically evaluate an RHD secondary prevention program led by a ministry of health in a contemporary, limited-resource setting. ADUNU is innovative in several other ways:

(1) As mentioned below, our design and effectiveness evaluation is based on an innovative application of an established HIV program assessment tool, the HIV treatment cascade, to RHD, similar to how it has been used for other health conditions.
(2) We have extended this treatment cascade to emphasize early diagnosis of RHD (the major bottleneck to widespread uptake of secondary prevention), moving echocardiography for RHD from research and pilot programs into routine clinical practice.

(3) This is the first use of modern implementation science methods and frameworks (described below) to evaluate an RHD program. ADUNU uses an array of implementation strategies to systematically address known barriers to care, ensuring that the model emerging from this project is effective in all parts of the country and is supported by key Ugandan stakeholders.

(4) ADUNU goes beyond the assessment of program effectiveness, costs, and cost-effectiveness to look at how the program would sustainably integrate within Uganda's primary healthcare system, strengthening the local response to cardiovascular diseases in general and creating a model for addressing complex chronic disease care in African countries.

(5) Our study provides new insights into ways that chronic disease care can be decentralized to improve access among marginalized populations (e.g., rural), with lessons for other diseases that could benefit from community-based testing.

4.0 IMPACT ON HEALTH

Historical RHD control programs in the Americas suggest that countries can, over the space of a decade, substantially reduce the health burden of RHD. Consequently, modelling studies support the notion that a two-thirds reduction in RHD disability and mortality in Uganda by 2040 is an achievable target that is comparable to current targets for control of infectious diseases (e.g., HIV/AIDS). To reach this RHD target, the Uganda MOH will need to, by the year 2030 (or sooner), deploy a national RHD program—informed by the success of ADUNU—that finds most Ugandans living with RHD and maximizes secondary prevention uptake and adherence. We anticipate that ADUNU will transform a centralized, passive care delivery model to a decentralized, active, and scalable model that will improve patient outcomes and strengthen healthcare in Uganda. The expected outcomes of this research are (i) a thorough understanding of the factors leading to success or failure of secondary prevention in low-resource settings and (ii) an innovative template for designing RHD programs that can be scaled nationally.

5.0 SUPPORTING PRELIMINARY DATA

Our understanding of the barriers to secondary prevention in Uganda comes from three studies that collectively form a comprehensive picture that justifies the approach used in ADUNU. Two published studies led by investigators Webel and Watkins used qualitative[8] and mixed methods[9] (respectively) to

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assess barriers from the patient and provider perspectives (respectively). In addition, Watkins recently led a qualitative study on the RHD care experience (manuscript in preparation). Table 1 presents the barriers that are consistent across these studies and shows their relative importance in the transcripts.

Table 1: Barriers to Secondary Prevention in Uganda

Type of Barrier	Relative Importance	Addressed by ADUNU
Systemic and Policy		
1. Medication and diagnostic shortages	+++	YES
2. Distance to RHD clinics (time and transport costs)	++	YES
3. Treatment delays and wait times	+	Partially
4. Lack of guidelines and registers for frontline workers	+	YES
Interpersonal and Individual		
1. Low awareness of RHD (patient and provider)	++	YES
2. Injection pain and fear	++	YES
3. Poor treatment by health workers	+	Partially
4. Disease stigma and lack of social support	+	Partially

ADUNU is an implementation science project that involves deployment of a programme based on two evidence-based practices, (1) secondary prevention of RHD, and (2) echocardiography-based diagnosis of RHD. To effectively implement these two evidence-based practices, ADUNU will use a range of "implementation strategies" that address the major barriers to care outlined in Table 1. These include: (A) securing MOH and DHO commitment to remediate district-level gaps in availability of medications and diagnostics by investing in supply chain strengthening and allocating sufficient budgetary resources to cover recurrent costs; (B) decentralising secondary prevention from distant referral hospitals to local HCIII, which are much closer to where patients live and have more trusted relationships with providers; (C) raising community, patient, and provider awareness of RHD and its risk factors to generate demand for testing services, encourage retention and adherence, and reduce stigma; and (D) deploying standardised guidelines for frontline workers, including best practices for minimising pain with BPG injection. Consistent with implementation science methods, the design of ADUNU will be adaptive, with opportunities to modify the implementation strategies throughout the course of the study to optimise delivery and address emerging challenges. The lessons learnt from this adaptive implementation will inform the guidance we provide to the MOH on how to scale the RHD programme across diverse districts around the country after the ADUNU study has ended.

In the last decade, our team has developed, tested, and refined the core components of ADUNU—based on the two evidence-based practices—in several research studies[10-13] and pilot studies. Over the last 3 years, we have also integrated these approaches, on a limited scale, into MOH facilities with excellent results, demonstrating that all components of ADUNU can be reliably executed by MOH providers in government health facilities. Specifically, we have shown that:

(1) Community sensitisation and mobilisation can reliably increase care-seeking behaviours and referrals for evaluations for acute rheumatic fever, the precursor condition to RHD.[14]

(2) Frontline nurses can obtain high-quality echocardiographic images that can be interpreted remotely, and echocardiography can be integrated into the workflow in busy government health facilities (e.g., antenatal care,[13] heart failure clinics[15]).

(3) Frontline nurses can rapidly screen large numbers of persons for RHD in school and community settings, averaging 2000-3000 persons screened per month (RHD case detection rate of 40-60 persons per month) in each district.[16]

(4) Secondary prevention can be integrated into the workflow of frontline nurses at Health Centres III, with very good retention and adherence rates (unpublished data from the GOAL trial, https://www.clinicaltrials.gov/ct2/show/NCT03346525).

6.0 STUDY OBJECTIVES

6.1 GENERAL OBJECTIVE

The overarching objective of this study is to evaluate the feasibility, sustainability, and public health impact of a district-based program (ADUNU) for secondary prevention of RHD in Uganda. This five-year study will be a demonstration project based in Amuru and Kitgum districts. The national MOH and local DHOs will implement ADUNU in these two districts, and investigator team will conduct an evaluation of the program. Lessons learned from the demonstration project will be used to refine and optimise the ADUNU model of care and, after the demonstration project has ended, scale it up nationwide.

Our evaluation of ADUNU will be informed by the Reach, Efficacy, Adoption, Implementation, and Maintenance (RE-AIM) framework.[17] RE-AIM facilitates a multi-dimensional understanding of the key elements of ADUNU—i.e., the "active ingredients" for public health impact—and since it is frequently used in implementation research can improve external validity. RE-AIM is recognised as ideal for evaluating public health

Table 2: Operational Definitions for Cascade Metrics

Cascade Metrics	Operational Definition	Notes
Diagnosis	Proportion of people living with RHD who have been diagnosed.	Denominator for metric is the established baseline population prevalence (2.0% in children <15 years, and 1.8% in those 15 years and older)
Enrollment	Proportion of people diagnosed who are enrolled into the RHD registry.	Requires attendance at an HCIV follow-up visit after positive screening
Retention	Proportion of people enrolled into the RHD registry who attend at least 2 HCIII visits in the past 12 months separated by at least 3 months.	Requires successful linkage to 'home' HCIII for secondary prophylaxis
Adherence	Days protected ÷ Days prescribed	Calculated as a continuous measure with each BPG injection providing 28 days of coverage.

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programs.[18] Core outcomes will be derived from the RHD "cascade of care," which is modeled after the HIV/AIDS cascade of care and includes "steps" for diagnosis, enrollment, retention, and adherence. Table 2 defines these outcomes and provides metrics that will be used in this study.

Our overarching hypothesis is that, over four years, ADUNU can effectively reach 50% of individuals with RHD (intensive district), and consistently achieve 90% registry enrolment, 90% retention, and 90% adherence (both districts). In other words, ADUNU can shift the care cascade from "0-0-0-0" (status quo) to "25-90-90-90" within two years in Amuru and to "50-90-90-90" within four years in Kitgum. Kitgum will be the first district in which ADUNU is deployed (second half of year 1), and Amuru will serve as a "replication" district in which ADUNU will be deployed at the beginning of year 3.

6.2 SPECIFIC OBJECTIVES

Objective 1: Demonstrate the impact of ADUNU, using the RE-AIM framework to assess program Reach,

Effectiveness, Adoption, Implementation, and Maintenance. Objective 1 has five sub-objectives:

a) Reach – Use echocardiography to increase the proportion of individuals with RHD who are detected, including identification of sub-groups not reached (target: 50% Kitgum district] or 25% [Amuru district] detected).
b) Effectiveness – Achieve goals in (1) registry enrollment (target: 90% of those diagnosed by RHD testing), (2) retention (target: 90% of those enrolled), and (3) adherence (target: 90% of those retained).
c) Adoption – Assess the proportion of healthcare facilities and providers that adopt ADUNU and understand barriers and facilitators to adoption success.
d) Implementation – Assess the proportion of healthcare providers and facilities demonstrating high fidelity to the relevant ADUNU components and protocols in which they have been trained and reasons for suboptimal performance.
e) Maintenance – Understand the (1) proportion of facilities and providers continuing to implement ADUNU as designed, and (2) sustainment of retention and adherence levels among individuals enrolled in the registry at 24 months post-introduction

Objective 2: Estimate the cost-effectiveness and budget impact of ADUNU. This objective will build on the first objective and will use standard methods for economic evaluation of health programmes.

7.0 STUDY METHODS

7.1 STUDY DESIGN

ADUNU is a non-randomised experiment, testing a strategy for implementing an evidence-based practice, decentralised RHD preventive services, in a new setting. It is a pre/post design (no control arm), but with no RHD programs currently in place in Amuru or Kitgum, the pre-intervention reality is that no patients in these selected districts have been diagnosed; meaning that the change seen over time in patient, provider, and program metrics will be the same as the point estimates for effectiveness of the various components of the program. This study design was chosen because it is the best strategy for evaluating the effectiveness of a complex intervention (including both case-finding and treatment components) in a setting without a pre-existing RHD programme; randomized and other quasi-experimental approaches would be unethical.

As mentioned previously, ADUNU uses a district-based healthcare delivery model that features the two core evidence-based program components: 1) population-based testing for subclinical RHD using echocardiography ("RHD testing"); and 2) continuous antimicrobial chemoprophylaxis ("secondary prevention") for all individuals found to have RHD. Appendix A21 is a detailed description of the ADUNU programme. Importantly, this programme will be implemented by the DHOs in partnership with the MOH. The study team will have no role in implementation; the focus of this ethics protocol is on human subjects research pertaining to the evaluation of the ADUNU programme that we will be undertaking. We will also provide technical support to the MOH in the design of the programme and will sit on a MOH committee focused on quality improvement/assurance of the programme but will not be involved in day-to-day operations.

RHD testing: This aspect of ADUNU involves the MOH implementing an organised programme through the DHOs to test district residents for RHD. All district residents aged 5-39 (when risk of RHD is highest and secondary prevention is most effective) will be eligible for RHD testing, to be conducted through

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echocardiographic screening by frontline healthcare providers in government health facilities. Four complementary approaches will be adopted to identify potentially undiagnosed RHD including:

(1) Testing of populations already at a HCIII for other care (i.e., opportunistic screening)
(2) Community testing including Health Fairs, multi-disease campaigns/events to target adults, children who are not school going and adolescents
(3) School testing targeting school going children
(4) Reactive testing targeting first degree relatives of people living with RHD

Registry-based secondary prevention at HCIIIs and HCIVs: A community-based RHD registry provides a clinical record system for case management and delivery of secondary prevention, tracks outcomes to improve the quality of care of delivery and identify systems problems like impending medication stockouts, and catalogues cases of RHD for epidemiological surveillance and research. As mentioned previously, the National RHD Registry is a reactive, centralised repository that is currently only used for research. The community-based registries that will be established in the two demonstration districts will interface with the National Registry and will be optimised for the three functions listed above. In each district, a physician and an RHD nurse coordinator at the HCIVs will provide case confirmation, counselling, and care coordination with linkage back to a home RHD registry site (HCIII) for secondary prevention. The district RHD coordinator will work closely with UHI to handle referral and counter-referral of participants who require specialised cardiology or surgical care.

7.2 STUDY SETTING

ADUNU will be conducted in Northern Uganda, where the prevalence of RHD is high (>2%). Research activities in the intensive district (Kitgum) will begin first and go on for most of the duration of this study, with work in the replication district (Amuru) starting in Y3 and having proportionally lower recruitment targets for feasibility. These districts were chosen because they are (1) geographically disparate within the Northern region, (2) have at least one highest-level health center (HCIV) to serve as the RHD coordinating centre, and (3) have no prior RHD-related activities. The ADUNU program will be led by the District Health Office (DHO) in each district. The 19 outpatient clinics in these districts that are capable of providing chronic disease care (HCIIIs) will provide a medical home for RHD registry-based case management and secondary prevention. In Kitgum, these will be the health center IIIs (Orom, Omiya

Anyima, Kitgum Maditi, Akuna Laber Health, Pajimo, Okidi, Mucwini, Loborom), Namokora HCIV and Kitgum General hospital. In Amuru district, these will include all HCIIIs (Bibia, Pawel, LacorPabbo, Pabbo, Pogo, Labongogali, Lacor (Amuru), Otwee, Kaladima, Olwal) and Atiak HCIV.

7.3 METHODOLOGY BY SPECIFIC OBJECTIVE

Overview

The proposed evaluation will follow a multiple-methods approach. We will collect a range of quantitative and qualitative data from different sources, including case management registries (health records), program documents (from the DHOs), provider surveys and observations, provider interviews, and patient interviews. Some data collection activities will involve human subjects, e.g., interviews of providers. Some data collection activities will not involve human subjects, e.g., review of program documents. This protocol and the methodology section emphasizes the components of the evaluation that involve human subjects. Table 3 lists the different groups of human subjects and target sample sizes for each group. Further details on specific research procedures for each group, by objective, are provided below. Additionally, we stress that we are *not* doing clinical research to test the effectiveness of secondary prevention and are *not* "enrolling" persons with RHD in the ADUNU program. The MoH is running the ADUNU program as a routine clinical activity, and we are evaluating it. The detailed list of activities in ADUNU package, which the MoH is implementing, is included in this protocol as Appendix A 21 but is *not* part of the research.

Table 3. Summary of participant groups.

Group	**Participant Type**	**Sample size by Objective and data collection type**	**Sampling frame and Inclusion criteria**
Groups A.1-5	Providers at participating HCIIIs and HCIVs in the two districts	A.1 Provider Surveys Objectives: 1c and 1e - N=50 A.2 Direct observation of Providers	For surveys and observation (A.1 and A.2), all providers will be invited to participate (19 from Amuru and 31

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		Objective 1d - N=50 A.3-A.4 Individual interviews Objectives 1c and 1d (A.3) - N=20 Objective 1e (A.4) - N=32 A.5 Time-motion study - N=21	from Kitgum) All providers will be eligible; selection will be based on maximum-variation purposive sampling focused on adoption (1c); fidelity (1d); and continued implementation (1e) For time-motion study one provider per facility will be invited to participate (11 from Amuru and 10 from Kitgum)
Groups B.1 & 2	Registrants (persons with RHD identified through screening)	B.1 Individual interviews Objective 1e - N=36 B.2 Out of Pocket Cost Surveys - N=42	Eligible patients will include persons enrolled in the RHD registry within 24 months of study completion (estimated 716); purposive sampling based on adherence outcomes A stratified random sample of patients will be selected from those enrolled in year 3 of the study. Sample frame

			will include 10 adults with RHD and 10 caregivers of minors with RHD from each facility (n=21).

Summary of qualitative methods

Objective 1 will involve substantial qualitative data collection across various sub-objectives and groups of participants. We summarise our general approach to qualitative data collection and coding here. We take a predominately positivist orientation, using in-depth interviews as needed to (i) explore and provide context for the quantitative data and (ii) substantiate claims that the program is being implemented as intended and is responsible for changes in clinical outcomes (i.e., causal inference). In other words, qualitative methods will help "answer 'why' or 'how' questions generated from preceding quantitative research."[19,20] Data collection will follow a sequential approach, with quantitative data given priority for assessing the main study outcomes and being collected first at each stage of the study.

The qualitative data we collect regarding Adoption (Aim 1c), Implementation (Aim 1d), and Maintenance (Aim 1e) will be informed by constructs from the Consolidated Framework for Implementation Research (CFIR).[21] CFIR was chosen as a complement to the main framework (RE-AIM) because it is well-positioned to help identify determinants of success or failure of adoption, implementation, and sustainment of outcomes in health programs.[18] We have a priori selected a subset of constructs from each of CFIR's five core domains (24 constructs in total) that are most relevant to ADUNU. These constructs will be used to develop the interview guides, Appendices A1 and A2 (using a development tool created by the CFIR collaborators) and will be used during coding and data analysis, following procedures recommended by Damschroder and Lowery.[22]

In-depth interviews with health workers and administrators will be conducted in English, and interviews with patients or community members will be conducted in the local languages.

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Following sampling of participants for each category as described above, interviews will be conducted by trained research nurses. Written informed consent will be obtained from all who agree to participate. Interviews will be conducted based on a semi-structured question guide. The interviews will take 30 to 40 minutes each. All interviews will be audio-tape recorded. The tape recorder will be stopped at the completion of the interviews and the participant debriefed, including answering any follow up questions they have. At the end of the interview, the participant will be thanked for their time and reimbursed before dismissal. After the subject is dismissed, the research nurse will fill out the field notes and ensure that that participant ID, date and location are recorded on the notes. The consent form, tape recorder, and field notes will then be placed in the pre-specified secured location at our program coordination office in the district. All in-depth interviews will be transcribed verbatim, translated into English as necessary, and then coded. Section 8.2 below outlines our general approach to qualitative data analysis.

Objective 1: Demonstrate the impact of ADUNU, using the RE-AIM framework to assess program Reach, Effectiveness, Adoption, Implementation, and Maintenance.

Over five years, the DHOs in the two study districts will implement ADUNU at MOH health facilities as described in the ADUNU Program Guide. Our research team will partner with the DHOs in health worker training and will provide technical and logistical support during implementation. While the core components of the two evidence-based practices (RHD testing and provision of RHD secondary prevention at HCIIIs) will be the same in Amuru and Kitgum, differences in supportive strategies (e.g., training frequency or the capacity of the district program champion) and contextual factors (e.g., patient receptiveness to screening and HCIII infrastructure) are anticipated.

The methods used in Objective 1 will allow for not only an assessment of within-district changes over time, but also a between-district comparison of the implementation of the ADUNU program. Aim 1 will entail an evaluation of the impact of ADUNU. Three types of data will be used in the evaluation: 1) routinely collected data (e.g., RHD registry data, facility and district administrative data), recorded by health workers and abstracted by research staff (de-identified), 2) quantitative, structured surveys and direct observation of providers, facilities, and patients, conducted by research staff, and 3) in-depth interviews of providers and patients. Objective 1 has five sub-parts, a-e:

Objective 1a (Reach)

Reach – This sub-objective will involve only secondary analysis of de-identified data collected by districts using routine MOH data collection procedures supplemented by some routine program data during the Ministry's rollout of the ADUNU Programme Package. As such, researchers from UHI, CCHMC, and UW will not collect or have access to identifiable health information for this sub-objective. We provide a brief overview of the types of data to be assessed below for further information.

The number of individuals screened and screening positivity rates will be extracted from screening logs implemented and maintained by DHOs and assessed by modality (school fairs, health days, passive health centre screening, and active outreach to family members of RHD diagnosed) to understand the relative efficiency and effectiveness of each screening approach in the implementation district. This data will be used to determine whether all or only a subset of screening approaches will be utilized in the replication district. Individuals who receive a positive indicator on screening are referred to their regional HCIV for confirmation. The rate of these referral completions will also be extracted from the routine DHO screening logs.

Patients who are confirmed as having RHD at the HCIV will be entered into the electronic ACT-registry platform and transferred back to their local HCIII for management of their care. The ACT-Registry platform has been rolled out across Uganda as the default care management system for RHD patients and has already received ethical approval from Makerere School of Medicine as part of the national RHD registry (Mak SOMREC 2013-072).

Objective 1b (Effectiveness)

Effectiveness – As with objective 1a, all data used for assessing objective 1b, the uptake and effectiveness of secondary prevention within the ADUNU Program, will come from abstraction of deidentified patient data from the electronic ACT RHD registry. This data is approved for use in research under a separate IRB approval from UNCST. (As a standard procedure, each HCIII will also have paper backup forms for use in the event of a power or internet failure. Data captured on these forms will be transferred into the electronic registry once the logistic issue has been resolved.)

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Program and registry data abstraction. Aims **1a** (Reach), **1b** (Effectiveness), and **1e** (Maintenance) will involve **secondary analysis** of data from the district RHD registries (i.e., proportion of registrants retained and adherent after 12 and 24 months) and related administrative data held by the DHOs regarding RHD testing activities (dates, number of participants, etc.).

Table 4. Examples of variables to be abstracted from RHD registries for secondary analysis.

Indicator	Frequency	Objective & Analysis Plan
# of individuals newly enrolled in the registry	Monthly	1b: Will be used in combination with screening data (Objective 1a) to calculate the proportion of individuals confirmed positive at HCIVs successfully enrolled in registry care management
Date and location of patient visit	Monthly	1b: Used to calculate the proportion of patients who have attended at least 2 visits at an HCIII in the last 12 months, separated by at least 3 months (retention)
Dates of patient's BPG injections since enrolment	Per-visit	1b & e: Used to calculate the proportion of days protected for secondary prevention
# of patients expected for BPG injection; # of BPG injection appointments missed	Monthly	1b & e: Used to assess implementation of program by health centre

Objectives 1c-e (Adoption, Implementation, and Maintenance)

In these 3 sub-objectives we will assess the extent to which the 6 health-centre-based clinical care components of the ADUNU program (1.3-1.5; 2.1-2.3 in the ADUNU Package) are successfully adopted, implemented, and maintained over a period of 24 months at HCIIIs and HCIVs. Our units of analysis will be both HCIIIs and individual providers of ADUNU.

Organizational-level: We expect initial adoption (Objective 1c) to be high (>90%) due to the characteristics of the intervention (i.e., deployed within all HCIIIs as a new health worker competency)

and the top-down management of public healthcare services in Uganda. We will deploy a brief quarterly survey with modules for facility administrators. These facility surveys will be filled out by providers who are acting as administrators of their health centre and will include questions on a range of logistic (e.g., availability of commodities and stockouts, basic infrastructure reliability) and organizational readiness topics (e.g., staffing levels and turnover, organization of patient scheduling, district support visits). They will not collect data pertaining to human subjects or capture any identifiers. Information from facility surveys will be complemented by analysis of routine programmatic indicators (e.g., # of healthcare workers trained on various aspects of RHD management). In addition to being reported quarterly to the MOH oversight group to inform program operations, changes in these measures from baseline will be assessed at 24 months post-roll-out in both the intensive and replication districts to understand maintenance (Objective 1e) of the intervention over time.

Provider level: Two types of data collection activities from frontline providers will be used to understand individual provider-level adoption (Objective 1c) and maintenance over time (Objective 1e): provider surveys and in-depth interviews of providers. The provider surveys will be collected quarterly, at the same time as the facility surveys to minimise data collection burdens on the research team and providers themselves. In contrast to the organizational-level data collection (above), the provider-level data collection will involve human subjects in the usual sense. All providers employed at HCIIIs and HCIVs (n=50) will be invited to complete the surveys. To assess ongoing provider fidelity to implementation of the core service delivery components of the ADUNU program (Objective 1d) we will also conduct direct observation of provisions of RHD care for each provider at least 6 months following completion of training and roll out of RHD activities at their health centre. Research staff will use a standardised checklist that will be developed from the core elements of RHD testing (e.g., ultrasound technique, saving of images) and secondary prevention (e.g., injection technique, adequate post-injection monitoring for anaphylaxis) as outlined in the ADUNU Program Guide and MOH standard of care clinical guidelines.

A sub-sample of providers will be purposively sub-sampled at 3 different time points (once for each of the 3 sub objectives) for in depth qualitative interviews. For Objective 1c, Adoption, the provider sample will be stratified based on their adoption survey responses (i.e., very high or low). For Objective 1d, Implementation, the provider sample will be stratified based on their fidelity scores during direct observation (i.e., very high or low). The target number for each round of interviews is 20, comprised of 8-

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10 interviewees per district. These interviews will be conducted at least 6 months after the deployment of the ADUNU Program in the intervention and replication districts (after at least 2 rounds of provider surveys have been completed). For Objective 1e, Maintenance, the provider sample will be stratified based on high and low levels of ongoing adoption of the implementation program components, with a target of 32 interviewees. These interviews will be conducted at least 24 months after the deployment of the ADUNU Program in the intervention and replication districts. See Sample Size Estimation below for more information.

For all interviews, subjects will be scheduled to participate in the interviews at a mutually convenient date and time. Interviews will take place at the clinics where subjects work but not during usual business hours. Each interview will be audio recorded. Following completion of the interview, the tape recorder will be stopped and the participant debriefed, including answering any follow up questions they have. At the end of the interview, the participant will be thanked for their time before dismissal. After the subject is dismissed, the research nurse will fill out the field notes and ensure that that participant ID, date and location are recorded on the notes. The consent form, tape recorder and field notes will then be placed in the pre-specified secured location.

Patient-level: To understand patient-level determinants of the ADUNU Programs long-term success (Objective 13 – Maintenance), we will also conduct a limited number of interviews (n=36) of registry patients in each district, stratified by adherence outcomes (see the Sample Size Estimation below for more information) as well as age group (children vs. adults). The guide for patient interviews is included in the Appendix- A 2. Since minors are not in a good position to participate in interviews regarding their healthcare, we will not be sampling minors or collecting data from them. Instead, we will interview their caregivers and obtain 'parental consent' from the caregivers to provide information on their child's healthcare experience. We will aim for approximately equally sized sub-samples of adult registrants and caregivers of minor registrants. These interviews will take place at least 24 months after the roll out of ADUNU in each district. A research nurse will utilize the RHD registry data records to identify individuals who meet the sampling criteria, and a list of potential subjects will be generated by the intervention study team at the Uganda Heart Institute. Potential subjects will be contacted by phone and invited to participate. Subjects will be scheduled to participate in the interviews at a mutually convenient date and time, usually at their health facility before or after a care encounter. Written informed consent

will be obtained from all individuals agreeing to participate. Each interview will be audio recorded. Following completion of the interview, the tape recorder will be stopped, and the participant debriefed, including answering any follow up questions they have. At the end of the interview, the participant will be thanked for their time before dismissal. After the subject is dismissed, the research nurse will fill out the field notes and ensure that that participant ID, date and location are recorded on the notes. The consent form, tape recorder and field notes will then be placed in the pre-specified secured location.

Objective 2: Demonstrate the cost-effectiveness and budget impact of ADUNU.

In parallel with the program evaluation (Objective 1), we will conduct prospective, activity-based costing of ADUNU. While we are primarily concerned with estimating costs from the health system perspective (as our target audience is the MOH), we will also collect focused data on out-of-pocket costs among a representative sample of registrants (i.e., costs from the patient perspective, one important measure of equity). Most of the economic evaluation is mathematical modeling that does not involve human subjects; however, there are two inputs to the modelling that involve data collection from human subjects, summarized below and represented by groups A.5 and B.2 in Table 3.

Cost analysis

To estimate program costs, we will adapt the standardised data collection instruments used in a study we did on RHD prevention and treatment costs in South Africa.[23] Our instruments will measure fixed and capital costs (e.g., facility rents, ultrasound machine costs, and in the short run, health worker costs) as well as variable or recurrent costs (e.g., drug costs per dose and transportation costs for outreach activities). Ingredients-based costing will be used for drugs and consumables, personnel costs, and equipment costs, whereas gross costing will be used for "indirect" costs such as facility rents and utilities and maintenance that are challenging to estimate using micro-costing methods.[24] Relevant data for ingredients-based costing include study data on participant healthcare utilisation (from the ACT database) and price lists of drugs, consumables, and equipment. DHO budget sheets for health facilities and overall health service utilisation (available in electronic District Health Information Systems software) be used for gross costing. The Global Health Cost Consortium reference case[25] will be used to guide the design of

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data collection instruments and methods used (e.g., valuation of capital items). Both financial costs and economic costs (including opportunity costs) will be measured.

As part of the program cost analysis, we will measure time spent by providers implementing the ADUNU programme. To obtain time use estimates, we will do a time-motion study using direct observations of providers at HCIIIs and HCIVs. We will adapt a data collection instrument we are currently using for the ADD-RHD study (REC REF: 2021-083) and administer it before and after the programme is rolled out in both districts (the pre-programme measurement is being done to establish changes in health worker time allocations). We will target a sample of 21 randomly selected providers, stratified by facility.

We will also estimate of out-of-pocket costs borne by registrants, which will allow us to estimate costs from the patient/household perspective. We will adapt a data collection instrument we are currently using for the ADD-RHD study that we have used successfully in Uganda in prior research (REC REF: 2021-083.[26] Since we have no a priori hypothesis to test regarding the magnitude or trend in out-of-pocket costs, we will target a sample of 42 randomly selected registrants, stratified by facility. As in the interviews for Objective 1e, we will stratify this sample into equally sized sub-samples of adult registrants and caregivers of minor registrants. Since there are no persons currently known to have RHD in these districts, we will not do pre-programme measurement of costs.

All human subjects costing data collection will be done over a three-month period during year 3, after the programme has been implemented for at least 12 months and patients and providers have had sufficient time to adapt their routines and workflows around this new healthcare delivery model.

7.4 DETERMINATION OF PRIMARY OUTCOME

Since this is an implementation study, not an epidemiological study, we have a series of primary outcomes across each of the objectives and sub-objectives. The main sample sizes and calculations presented below are based on our proposed secondary analysis of the RHD registries that will be set up in the two districts.

Care cascade outcomes data will be extracted via retrospective review of the RHD registry at each HCIII with cross-verification of RHD registry reporting at the district health office (DHO), which happens

quarterly. For Objective 1, RHD will be defined as evidence of RHD on confirmatory echocardiogram, typically but not exclusively, following a positive screen during RHD testing (i.e., patients who present clinically with signs/symptoms of RHD and have a confirmatory echocardiogram will also be included). RHD care metrics will be defined as follows: (1) Diagnosed = proportion of people living with RHD who have been diagnosed with the denominator the established baseline population prevalence (see below), (2) Enrolled = proportion of people diagnosed who are enrolled into the RHD registry (requires attendance at a HC IV RHD clinic visit), (3) Retained = proportion of people enrolled into the RHD registry who attend at least 2 HC III visits in the past 12 months separated by at least 3 months, (4) Adherent = at least 80% calculated as continuous days of coverage, days protected / days prescribed (with each BPG injection providing 28 days of coverage).

The care cascade outcomes will help to establish "effectiveness" (Objective 1b) and "maintenance" (Objective 1e) of ADUNU, which will. We will also keep track of other quantitative and qualitative outcomes relating to Objective 1a, Objectives 1c-1d, and Objective 2 as described below. While all of the outcomes are important from an implementation research standpoint and are therefore "primary," the cascade metrics can be considered the principal metrics from a clinical standpoint and are emphasised in this protocol.

8.0 STATISTICAL ANALYSIS PLAN

8.1 Sample Size Estimation:

Secondary analysis of registry data. Objectives **1b** (Effectiveness) and **1e** (Maintenance) will involve quantitative analysis of registry data among individuals enrolled in the district RHD registries. Based on a target Reach of 50% (Kitgum) and 25% (Amuru) of persons with RHD by the end of the study and an assumed prevalence of 2.0% in children and 1.8% in adults, we expect that 2168 persons will have been enrolled for 12 months by Q2 of Year 5 (See Table 5 below), the endpoint for Objective 1b, and 845 persons will have been enrolled for 24 months by Q3 of Year 3, the endpoint for Objective 1e.

Table 5: Estimated total populations of Amuru/Kitgum districts and projected cases per age-group

District	Total population, all ages	Est. population, 5-39 years	Est. population, 5-14 years	Est. RHD cases, 5-14 years	Est. population, 15-39 years	Est. RHD cases, 15-39	No. of HCIIIs	No. of HCIVs

						years		
Kitgum	226,700	155,000	63,500	1,270	91,400	1,640	9	1
Amuru	222,000	151,000	62,200	1,240	89,500	1,610	10	1
Both districts	448,700	306,000	125,000	2,510	180,000	3,250	19	2
*Utilizing RHD Prevalence in children <15 year of 2.0% Definite or Borderline RHD (WHF criteria), and between 15-39 years of 1.8% Definite RHD (WHF Criteria), HCIII: Health Center 3, HCIV: Health Center IV								

If we assume a target of "50-90-90-90" (diagnosis-enrollment-retention-adherence) can be achieved, and a baseline RHD prevalence of 2.0% and 1.8% in children and adults respectively, a sample of 1844 individuals diagnosed across the two districts provides us with a +/- 2% margin of error at each level of the cascade of care, e.g., adherent proportion would be 90% (95% CI: 88-92%) of those retained in care. Because the pre-programme proportions along the care cascade are expected all to be zero (no prior RHD activities or National Registry participants from these districts), the "effect sizes" for ADUNU are identical to the proportions estimated along the cascade at 12 months.

For assessment of maintenance, we assume a non-inferiority margin of less than 5% of the baseline value is clinically significant. With a target of 716 individuals diagnosed with RHD by the third quarter of year 3 and thus able to provide 24-month follow-up data by the third quarter of year 5, our sample has 98% power to detect a non-inferiority margin of 5% from baseline for adherence (adherence being the last step in the cascade and thus the lowest sample size); using the exact test for non-inferiority of one proportion and a one-sided alpha of 0.025.

Provider surveys and direct observations. Objectives **1c** (Adoption), **1d** (Implementation), and **1e** will also involve quantitative data collection from providers using a standardized survey instrument on Adoption and a standardized checklist on implementation fidelity that will be completed by the research staff via direct observation. All providers (**n = 50**) will be invited to participate. Provider data collection will occur in parallel with the facility surveys and at the same frequency (quarterly or annually, depending on sub-objective).

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Provider interviews. A subset of providers will be invited to participate in in-depth interviews relating to Objectives **1c**, **1d**, and **1e**. For all sub-objectives, we will use maximum variation purposing sampling to capture high and low performers, stratified by district. The sampling frames in the three sub-objectives will be slightly different based on the specific research questions:

- For Adoption, we will sample 5 high and 5 low adopters from each district **(n = 20)**
- For Implementation, we will sample 20% of providers with the highest fidelity scores and 20% of providers with the lowest fidelity scores (per the checklists used in **1d**), again, stratified by district **(n = 20)**
- For Maintenance, which is likely to be influenced by ongoing facility-level adoption and implementation, we will identify the two highest- and two lowest-performing facilities in each district (8 facilities in total) at the end of ADUNU (per their scores on the implementation fidelity checklists used in 1d) and will sample the 3 providers and the administrator at each of these 8 facilities **(n = 32)**

For Objectives 1c-1d, a sample size of 20 providers should give us sufficient thematic content to understand the drivers of adoption and adherence and triangulate the quantitative data collected in these objectives (facility surveys, providers checklists, etc.). Because Objective 1e is central to understanding the long-term success of the programme from the provider perspective and patient perspective (see below for latter), we are planning for a larger sample to ensure thematic saturation. For both sets of interviews, we anticipate inviting 1% of the extreme cases for an interview (e.g., n= 18 least adherent and n=18 most adherent patients; total N~36). Based on Webel's extensive experience conducting mixed methods studies, this sample size is sufficient to achieve the descriptive qualitative objectives.

Registrant interviews. A subset of registrants will be invited to participate in in-depth interviews related to Objective **1e**. We will use maximum variation purposive sampling to capture registrants exhibiting high and low adherence, stratified by district **(n = 36)**. (See justification for sample size in previous paragraph.) As mentioned in the Research Strategy, we acknowledge that interim analysis of registry data may reveal shortfalls in certain facilities or sub-groups of registrants. if this is observed to be the case, we will conduct additional qualitative data collection based on interim Effectiveness data (**1b**) and in collaboration with the TAQA. The goal of this data collection will be to identify and remediate any emergent barriers

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that necessitate additional tailoring of ADUNU; we will request IRB modifications before engaging in these interviews.

Aim 2 costing data. We anticipate that we will estimate the cost and cost-effectiveness of the ADUNU programme using mechanistic approaches (e.g., Markov state-transition model) rather than statistical approaches. Hence the rationale for sampling in the time-motion study and out-of-pocket cost survey is to establish a range of plausible values (to be varied in model-based sensitivity analyses) rather than achieve some target level of statistical significance. As such, we plan to observe 21 providers, with one randomly sampled from each facility, and to survey 42 registrants, with two randomly sampled from each facility. Based on our previous experience conducting costing studies, these sample sizes should be sufficient to achieve a reasonable level of precision in average provider time and patient cost values (respectively) without placing undue burden on research staff, who will be primarily concerned with collecting data for Objective 1.

8.2 Primary Outcome - Analysis Plan:

Objective 1

Qualitative data analysis

The development and application of a coding scheme will be an integral component of the data analysis process. It will enable systematic examination and interpretation of the data related to the primary analytic foci. The coding scheme is conceptualized as a multilevel structure. At the highest level are the primary analytic foci coded as headings; in the proposed study, these will address the barriers and facilitators of widescale uptake and adherence to the ADUNU intervention. Specific aspects of the headings are assigned core codes. Specific aspects or dimensions of the core codes are assigned sub-codes. We will use Dedoose, a cloud-based qualitative analysis program, to facilitate analysis. The following 7 steps will be used to develop the coding scheme by a coding team of 2-4 trained investigators led by co-I Webel:[27],41,8 Step 1: Identify the principal issues discussed by participants; Step 2: Construct definitions of the primary analytic themes; Step 3: Develop and apply core codes and sub-codes to the initial set of interviews; Step 4: Develop a provisional coding scheme; Step 5: Test and refine the provisional coding scheme; Step 6: Reconcile coding differences and construct an updated and final coding scheme; Step 7: Apply the coding scheme to the full data set and assess inter-coder reliability. After all transcripts have been coded, we will

extract and examine the content of text segments linked to core codes and sub-codes relevant to understanding barriers and facilitators of ADUNU. Based on the coded data, we will propose ways in which certain themes are analytically related. A careful examination of the coded text will reveal the associations among these themes and may lead to more refined data searches. Once we establish patterns of relationships among themes and issues, we will identify participants' accounts that support or refute these patterns. Identifying and accounting for cases that deviate from an interpretative pattern enables us to test and confirm the pattern's validity and robustness. As described below, the coded data resulting from each sub-Aim will then be mapped back to CFIR to improve transferability. The qualitative interview data will be intrinsically integrated with the quantitative data collected and will be presented accordingly.

The team will adhere to qualitative research processes to ensure the credibility, confirmability, dependability, and transferability of the qualitative data from these analyses.[28] To support the credibility of the data, we will conduct peer debriefing and triangulate findings across multiple data sources (i.e., surveys, interview data). In addition, we will use "member checks," i.e., sharing of initial data interpretations with participants to ensure accurate interpretations. Triangulation of findings, along with reflexivity, will enhance the confirmability of the interpretations. The investigators will carefully record an audit trail and keep extensive field notes to facilitate transferability of study findings into other contexts.

Quantitative data analysis

Objective 1a. Descriptive statistics will be used to calculate the proportion of estimated RHD cases (based on prevalence studies in nearby districts) able to be identified by RHD testing, stratified by district and participant demographic characteristics.

Objective 1b. We will compute descriptive statistics on participant outcomes along the RHD care cascade to determine whether we have met our target of "90-90-90" and will conduct logistic regression analyses to identify factors associated with better enrolment, retention, and adherence. Because the pre-intervention proportions along the care cascade are expected all to be zero (no prior RHD activities in these districts),

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the effect sizes for our intervention are identical to the proportions estimated along the cascade at 12 months.

Objective 1c. We will compute descriptive statistics on the proportions of facilities and staff who have adopted ADUNU using an adoption survey in Appendix A3 and use logistic regression to identify sub-groups (e.g., RHD testing vs. secondary prevention staff) or factors predicting high adoption.

Objective 1d. We will compute descriptive statistics to quantify implementation fidelity (i) at the provider level, using a simple scoring system (proportion of checklist items correctly executed- see Appendix A4), (ii) at the facility level, using a similar scoring system based on facility survey results, and (iii) at the district level (i.e., population-weighted average of facility measures).

Objective 1e. We will calculate the proportion of providers and facilities still implementing ADUNU 24 months post introduction- see appendix A2 (target: >95%) and explore predictors of attrition using logistic regression. Similar to Aim 1b, we will construct a follow-up cascade of care among the subset of patients who have been enrolled for at least 24 months. Statistical analysis of patient-level data in the care cascade will be framed as non-inferiority of outcomes at 24 months as compared to outcomes at 12 months. .

Synthesis of qualitative and quantitative data from Objective 1: We will compile quantitative measures for each of the five sub-Aims into one matrix, stratified by district, to summarize the overall impact of the program and identify strong and weak points in initial and sustained implementation. Coded qualitative data will provide additional insights into strengths and weaknesses of the program and factors that led to extreme or unexpected quantitative findings. As ADUNU is a non-controlled, non-randomized experiment, the qualitative data can also shed light on potential causal effects on patient outcomes. For example, data from Objective 1d will be used to show how varied implementation might have led to varied patient outcomes (Objectivess 1b and 1e). Similarly, patient interviews in Objectives 1e will help determine whether ADUNU had its intended effects on health-seeking behaviour. This synthesis will support claims regarding health impact, feasibility, and sustainability of the ADUNU Program Approach and thus national-level impact beyond the study period.

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Objective 2

Cost analysis

Time-motion study. We will compute descriptive statistics to estimate the average time that providers spend providing secondary prevention services to each registrant (see appendix A7). Average time per visit will be multiplied by the average number of visits per registrant per year and then by average health worker salary to estimate the health worker time cost of the ADUNU programme. These data, which focus on time spent in clinic, will be combined with programme records regarding non-clinic activities (e.g., outreach screenings and administrative time) to arrive at an estimate of the overall cost of the programme per registrant per year (and per 100,000 population per year).

Out-of-pocket cost survey. We will compute descriptive statistics to estimate the average out-of-pocket cost per visit among registrants receiving secondary prevention services (Appendix A6). These data will be multiplied by utilisation rates to arrive at an estimate of the out-of-pocket cost of the programme per registrant per year.

Cost-effectiveness analysis and budget impact analysis

Assessing the incremental cost-effectiveness of ADUNU thus requires a natural history model, and assumption of zero costs, for the "comparator" scenario in a cost-effectiveness analysis (CEA). We will adapt a published CEA tool[29] that includes a natural history outcomes model that will be calibrated using local prevalence and mortality data estimates from our previous research.[30] Incremental improvements in long-term health outcomes like RHD complications and mortality will be extrapolated from incremental improvements in secondary prevention uptake and adherence as measured in Aims 1b and 1e. Again, a health system perspective on costs will be taken, with analytic time horizons of 10 years (i.e., an average policy cycle) and 100 years (i.e., lifetime costs and benefits). Incremental cost-effectiveness ratios will be computed based on estimates of average program costs per participant and average improvements in clinical outcomes per participant compared to the status quo, i.e., no care. Standard practices in discounting and sensitivity analysis will be used and reported according to guidelines.[31]

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Alongside the CEA, we will conduct a budget impact analysis (BIA) to support budgeting and medium-term financial planning. We will harmonize our cost modelling with the budget projection models used by the national MOH and DHOs for the healthcare system in general to ensure comparability and integration. The final product of the BIA exercise will be a district-level planning tool that will (i) produce estimates of annual program costs per capita of the "scalable unit," including estimates of resource quantities for by key components (e.g., nurse FTE, vials of BPG), and (ii) a semi-quantitative rapid assessment of potential bottlenecks (e.g., drug supply chain). The BIS will also include several scenario analysis related to uncertainty in key parameters and will be reported in accordance with established guidelines.[32]

9.0 DATA MANAGEMENT PLAN

9.1 Data collection

The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data. Most data entry will occur though a tablet-based CRF's using the REDCap platform (a secure web-based data storage application), which can be used when connected to the Internet. In the event that electronic data is not able to be entered, paper CRFs will be available for use and will be transcribed to the electronic form as soon as ability is restored.

9.2 Data capture methods

Electronic data capture will be used for all aspects of this study, except for consent/assent, which will be done through paper forms. Data entry and storage will be completed by study staff using the online REDCap platform. All users will be assigned unique log-in and passwords and access to identifying information will be restricted based on individual user's role and needs. Data will be entered in real time. On a regular basis, a research assistant will perform data entry quality checks, and built rules will ensure nonsense data (ages outside the range, etc.) cannot be incorrectly entered. Mandatory field completion will ensure all required data is collected.

9.3 Data storage

Study data will be entered directly into REDCap supported cloud-based research information system that provides form-based data entry. Content, validity and consistency rules will be applied to data entry fields to ensure completeness and accuracy of data. In the event of internet unavailability, paper back-up forms

will be available and double data entry will be used to ensure data quality. All information will be encrypted, and all reasonable efforts will be made to keep information private and confidential. Paper records and consent/assent will be kept in a locked research cabinet at the study offices or in the research office of the UHI.

9.4 Record retention

Data will be kept for at least 15 years after the completion of the study, or until the 25th birthday of the youngest participant, whichever is later, in accordance with the requirements of the Therapeutic Goods Administration and Health Privacy Principals. Paper records and consent/assent will be kept in a locked research cabinet at the Uganda Heart Institute. Online data will be maintained on the web-based REDCap platform. After study completion only the co-principal investigators will retain data access rights. At the end of the archival period, the co-principal investigators will ask the Cincinnati Children's Hospital Medical Center to erase the online records and the team will shred and dispose of paper records.

9.5 Quality control and quality assurance

A standard operating procedure (SOP) will be developed for the assurance of quality control and quality assurance activities. The investigators will have responsibility for ensuring both are maintained throughout the study period. The research coordinator will manage the routine oversight of these areas including:

- Review of all consent/assent documentation to ensure proper completion and filing of paper forms.
- Monthly review with each case manager to ensure protocol compliance of all enrolled participants.
- Monthly review of 25% of electronic data forms to ensure completeness for the first 3 months of the study then monthly review of 10% of records to assure quality.
- Jointly, one of the co-principal investigators and the research coordinator will address any identified quality issues through re-training of involved staff and will develop a written corrective action plan when needed.
- All identified protocol violations will be reported to the IRB within 30 days of identification.
- All involved research staff will receive detailed training and competency testing on the protocol and SOP. Training will be conducted by the senior research staff and documented through a certification of completion, maintained on site in the research offices.

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10.0 STUDY ADVISORY BOARD

We will convene an external ADUNU Advisory Board composed of representative members of key stakeholder groups shown here including Ugandan government officials (representatives from the MOH among others), additional representatives—independent of study investigators—from the two US Research Institutions (Cincinnati Children's and University of Washington) that have had longstanding collaborations in Uganda, other global NGOs (including Reach, the global technical organization for implementation of the 2018 World Health Assembly RHD Resolution), and people living with RHD. The advisory board will meet yearly to monitor study progress, to provide perspectives on how to overcome challenges to meet milestones, and to think strategically about the post-intervention phase. We envision that some of these advisory board members would be willing to serve on a Uganda MOH working group after the study is concluded. This working group would seek funding from government and non-governmental sources to scale the project, pending a report on the cost-effectiveness and budget impact generated by Aim 2. We have taken a similar approach to the maintenance phase of RHD control in Uganda after our RHD Action project.

In addition, this study will make use of a novel governance structure, the Technical and Quality Assurance (TAQA) working group. The TAQA will oversee implementation of the ADUNU program within the MOH Rheumatic Heart Disease Advisory team (led by Director Clinical Services, MOH); it is not a part of the research study per se and will not provide advice on the research.

Membership in the TAQA will consist of at least one individual from the following designations:

- MOH Directorate of Clinical Services (Non-communicable Diseases Department)
- MOH Department of Quality Assurance
- MOH Non communicable Diseases Department.
- National Medical Stores
- District Health Office representative (1 per district participating)
- Patient representative (person living with RHD)
- ADUNU PI team (Okello, Beaton & Watkins)

The TAQA will be tasked with providing quarterly oversight of implementation roll-out, with a focus on emerging district- and facility-level barriers that threaten patient outcomes, such as (1) uptake and efficiency of RHD testing, (2) linkage to care, retention in care, and medication adherence, and (3) adverse events among registrants; as well as recommending strategies to minimize the impact of persistent system challenges that may impede scale up, including supplies of essential medications and diagnostics (e.g., benzathine penicillin and echocardiography machines). The TAQA will review quarterly data from the district registries and provide feedback to help remediate emerging implementation challenges. This responsive design will not only provide timely support for program delivery within the study, but will also allow ADUNU to identify effective, feasible adaptations available in response to determinants of success for use by the MOH in future scale-up efforts.

11.0 TIMELINE

Table 6. Timeline

	Year 1				Year 2				Year 3				Year 4				Year 5			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Enrollment Timeline																				
District 1 Kitgum District: (Intensive)		Training			Target 50% Reach															
District 2 Arua District (Replication)									Training				Target 25% Reach							
Cummulative RHD Case Detection																				
Total Pediatric Case Detection (2% prevalence)			25	51	102	153	204	255	306	384	462	567	672	776	881	986	1091	1196		
Total Adult Case Detection (1.8% prevalence)			14	28	56	85	113	141	169	211	254	310	366	423	479	535	592	648		
Cumulative Pediatric and Adult RHD Cases			39	79	158	237	317	396	475	595	716	877	1038	1199	1360	1521	1683	1844		
Recruitment and Analysis																				
Recruitment Targets Met											1e							1a, 1b		
Analysis (interim light blue, final dark blue)							1a, 1b	1c, 1d		2		1e	1a, 1b		1c, 1d	2		1a, 1b	1e	

12.0 POTENTIAL LIMITATIONS AND ALTERNATE APPROACHES

While ADUNU has been designed to address the major secondary prevention implementation determinants and barriers to RHD care in Uganda (e.g., distance to healthcare, provider training, medications, and diagnostic supplies), it can only partially address "upstream" barriers, including those related to poverty and access to healthcare in general. Specifically, ADUNU will reduce (by bringing care closer to home) but not eliminate economic barriers (inability to miss work, pay for transportation, etc.),

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remediate (through community messaging campaigns) but not solve low health literacy, and strengthen (through partnership with TAQA, DHOs, and the MOH) but likely not perfect the BPG supply chain in participating districts. Future research studies could be designed to make additional improvements to the core ADUNU model based on learnings from this project.

There may be unforeseen challenges in rolling out RHD testing that could hinder our achievement of the Reach targets of 50% and 25% as well as persistent challenges in maintaining high performance along the cascade of care. We detail a variety of scenarios in the Statistical Design and Power document, showing good precision in cascade metrics, including durability of outcomes (Objective 1e), even under 'worst-case' scenarios. We stress that "50-90-90-90" is merely a target, not a prerequisite for claiming effectiveness. Given the current standard of "0-0-0-0," incremental improvements in case detection and care would still be game-changers for individuals affected by RHD, who currently lack access to life-saving services. Again, with support from the MOH, the TAQA will track quarterly metrics to identify and remediate emergent challenges (see section 10 above).

Our pre/post study design presumes no previously identified cases of RHD in the two districts, which we acknowledge is unusual but is substantiated by review of National Registry data (based at Uganda Heart Institute, the sole provider of cardiology care in Uganda) and the fact that no RHD diagnostic capacity exists in the study districts. To address the possibility of some previously identified RHD cases in the districts and the effect this might have on our pre- vs. post-implementation estimates of the cascade of care, the DHOs' RHD testing intake form will ascertain whether a participant has been informed of a diagnosis of heart disease, including RHD. We will request full medical records for any participants who answer yes, including verification of RHD diagnosis by echocardiography. Any individuals with previous RHD diagnosis will be added to the dataset and their data used to adjust the pre- vs. post-implementation estimates for Objectives 1b and 1e.

The ADUNU evaluation focuses mostly on utilisation patterns and intermediate outcomes like adherence. However, ADUNU will also create the structure, alongside the MOH, to track clinical outcomes, including RHD hospitalizations and deaths among registrants. These data, more fully captured through longer follow-up and subsequent studies, will provide some of the highest quality epidemiological data on the impact of RHD across the severity spectrum (majority of prior global data from severe cases, coming

to clinical attention when patients are symptomatic and experiencing complications), and provide an invaluable dataset for additional clinical and implementation research.

13.0 RISKS AND BENEFITS

Potential risks

Risks associated with participating in the proposed research

Loss of confidentiality. The risk associated with gathering mixed methods data from participants by properly trained and supervised research assistants and technical staff is low but does include the risk of loss of confidentiality.

Psychological risks. We do not anticipate any substantial psychological risks to be associated with participation in this study. As part of our assessments, we will ask participants about their demographic characteristics (i.e., education, marital status, or in some instances income). It is possible that some participants may feel uncomfortable answering some of these questions. We will only ask questions that are relevant to our study objectives (i.e., evaluation of the ADUNU program), and we will inform patients that they may refuse to answer any interview questions, but still be involved in the study. It is also possible that participants may be uncomfortable talking with the research assistant about some topics that are included in the interview. We have not experienced any significant issues regarding this in our prior qualitative or mixed-methods studies with RHD. However, subjects will be permitted to skip any topics that make them feel uncomfortable, and subjects will be informed that if they choose to discontinue the study at any time, this will not interfere with their usual medical care.

Additional patient risks associated with participating in the MOH-led ADUNU programme

Below are risks that individuals will incur if they choose to participate in RHD testing and clinical care. These are not risks associated with our *evaluation* of ADUNU. They are risks related to receiving RHD services by the MOH, with which our study team is not directly involved. These risks will be outlined in

the general consent for medical care that MOH staff will obtain (e.g., when obtaining clinical consent for RHD testing). We mention them here for comprehensiveness.

RHD testing. Echocardiography is not associated with any known risks. Detection of RHD could result in emotional distress.

Detection of clinically significant problems. Although not caused by study participation, it is possible that other clinically significant problems will be detected by study staff or during RHD testing. Registrants or community members suspected of a significant non-RHD cardiac issue will be referred to the HCIV or district hospital for evaluation as per standard protocols within the community health system.

Benzathine Penicillin G (BPG) allergy or anaphylaxis. Every 28-day intramuscular BPG is the standard of care for patients diagnosed with RHD.[33] International data suggests the incidence of allergic reaction to long-term BPG prophylaxis is 3% and the incidence of anaphylactic reaction is 0.2%.[34]

Other medication side effects. All medications have potential side effects. Medications used in this study will only be prescribed by a healthcare provider (nurse or clinician) according to his/her best clinical judgement and approval. Common side effects of medications used to treat more advanced RHD include but are not limited to bradycardia, lightheadedness and orthostatic hypotension, lower extremity edema, kidney injury and electrolyte imbalances.

Potential benefits

Potential benefits for subjects may include diagnosis with RHD and linkage to guideline based RHD care, with a consequent reduction in risk of RHD progression. In our previous experience, subjects in echocardiographic screening studies have generally found participation to be a positive experience and they often feel good about helping provide information that has the potential to help others like them. Potential benefits to others include the possibility that this research will lead to the development of more efficient and effective strategies for improving the uptake of secondary prevention in low resource

settings, which would lead to consequent reduction in subsequent, cardiovascular complications and death. Given the minimal risks associated with this research, and the potential benefit of the proposed findings, the risks to subjects are reasonable, especially with our plan to protect subjects from these risks. As this is a pragmatic study of an intervention implemented in routine clinical practice, subjects (individuals receiving RHD testing and secondary prophylaxis) will not be reimbursed for their time spent on study participation, as this constitutes a financial incentive that probably cannot be sustained when the programme is scaled nationally.

For decades, WHO has recommended registry-based care for people living with RHD,[35,36] yet there is no example of a successful national RHD registry program in a low-income country. There is an urgent need to demonstrate the feasibility, uptake, and cost of integrated, community based RHD programmes in low-income settings to inform the development of National RHD Action Plans and improve outcomes for people living with RHD. This study may establish the effectiveness of a multi-component implementation science intervention for RHD that can be disseminated widely. This multi-component intervention has the potential to be disseminated very broadly in clinical settings in sub-Saharan Africa, because of the potential for improved outcomes among people living with RHD. The health risks to participants are offset by the potential benefits to them and to society.

14.0 ETHICAL CONSIDERATIONS

Research Ethics Approval:

This research will be reviewed and approved by the research and ethics committee(REC) at the Uganda Heart Institute and the Uganda National Council for Science and Technology (UNCST). Additionally, we will seek administrative clearance from the district and local authorities prior to implementing this program. We will also seek reliant reviews as indicated from the IRBs at Cincinnati Children's Hospital and the University of Washington in Seattle. For institutions where researchers will have no access to identified patient information (Children's National Medical Center), we will seek a waiver of IRB review. All research staff and investigators will complete the approved Human Subjects training on "The Ethical Conduct of Research with Humans" at all participating universities and institutions.

Informed Consent/Assent:

A mix of methods (direct education, public health messaging, and public notices) will be used by the DHO to recruit community members for RHD testing. As outlined, testing will occur at school-based and community-based health events as well as being offered during routine medical appointments, or by invitation. Community members presenting for RHD testing will participate only after appropriate informed consent/assent procedures, which will be handled by the DHOs and local providers as per guidelines for obtaining consent for clinical care.

We will use the RHD registry at all the potential study sites to identify potential subjects to participate in the qualitative and patient out-of-pocket cost components of our study. Potential subjects will initially be contacted by a research assistant by a phone call. Following a telephone script, the research assistant will describe the study in detail, ensure the patient is eligible, and schedule a baseline study visit. All subjects participating in the above-mentioned study components will give informed consent to participate. Consent forms will be written in English and translated into Luo, the local language in Amuru and Kitgum districts. Translating the consent forms to Luo will allow persons who cannot comprehend English to participate in the study. Research Assistants will read, review, and discuss consent forms with all potential participants prior to asking them to sign. If the candidate appears confused or indicates a lack of understanding, the interviewer will attempt to identify the misunderstanding and to explain the form.again. Any candidate who still does not demonstrate adequate comprehension of the form will be excluded from the study. We will ask questions to confirm understanding of the material covered in the consent procedure, both open-ended (e.g., "Could you tell me what's going to happen if you enroll in the study?") and closed (e.g. "Will you get free medications from the staff of this research study?). Interviewers will witness and date the signed forms and complete the corresponding. We will utilize an Informed Consent checklist to document the participant's understanding of the informed consent process. Consent procedures will take place in a private room or office. Consent forms will be kept in a locked file cabinet within a locked room.

Draft consent forms (English) are provided in appendices A8-A14. These forms will be translated into the relevant local languages and re-submitted for IRB approval stamps after the main study protocol has been approved.

Protocol Modifications:

ADUNU will be conducted in compliance with the current version of this protocol. Any change to the protocol document or Informed Consent Form that affects the scientific intent, study design, patient safety, or may affect a participant's willingness to continue participation in ADUNU is considered an amendment, and therefore will be written and filed as an amendment to this protocol and/or informed consent form. All such amendments will be submitted to the above-named regulatory bodies, for approval prior to becoming effective.

Confidentiality:

The following confidentiality-protection steps will be taken: (1) All research staff will participate in initial training, follow-up training, and ongoing monitoring and supervision to ensure their understanding of ethical issues involved in this research; (2) consent forms will be maintained in locked files with limited access, separate from any subject data and will only be accessible to the study team; and (3) any personal identifiers linked to data will be removed and replaced by code numbers in all records. These steps are not foolproof, and participants will be informed of the associated risks at the time of informed consent.

Research staff will spend approximately 20 hours in initial training sessions and observed practice. Training includes reading and discussing research protocols and selected articles about interviewing, tracking, participants and attending lecture sessions regarding emergency procedures, mandatory reporting, confidentiality, and research ethics. Training also will include how to handle transient discomfort or distress related to embarrassing or sensitive discussions as well as how to identify and respond to signs of acute distress; experienced supervisors will be available for immediate consultation in the event of unexpected acute psychological problems; and all staff will be made familiar with referral resources and procedures for psychological, social services, and other emergency needs.

Financial Disclosure:

The research team have no significant financial interests to declare.

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16.0 APPENDICES

ADUNU Workplan

		Year 1		Year 2		Year 3		Year 4		Year 5	
Kitgum	Pre-Launch Period										
	Project Launch Period										
	Health worker Training										
	Data collection										
	Mid-term data analysis										
Amuru	Pre-Launch Period										
	Project Launch Period										
	Health worker Training										
	Data collection										
	Data analysis										
Disseminantion											

ADUNU Budget

	Year 1 (US $)	Year 2 (US $)	Year 3 (US $)	Year 4 (US $)	Year 5 (US $)	TOTAL
Personnel	110000	136000	170000	171243	140624	727867
Travel	14000	16000	8000	8000	10500	56500
Materials and Supplies	6000	9000	15800	15000	15000	60800
Administration	10000	18000	7000	6500	14000	55500
Results dissemination	0	0	0	0	3000	3000
Other	1000	3000	3000	2000	4000	13000
Contingency	3000	3000	3000	3000	4500	16500
Reimbursement	10000	16920	19900	24100	25913	96833
Total	**154000**	**201920**	**226700**	**229843**	**217537**	**1030000**