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Implementation of a dynamic mobile application to enable community-based decentralization of rheumatic heart disease case management in Uganda: a study protocol

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ABSTRACT:

Introduction: Rheumatic heart disease (RHD) affects more than 39 million people worldwide, most of whom live in low- and middle- income countries. Secondary antibiotic prophylaxis (SAP), given every 3 to 4 weeks as intramuscular benzathine penicillin G (BPG), can improve outcomes, but only if more than 80% of doses are received. Poor adherence is strongly correlated with the distance patients need to travel to receive prophylaxis. Decentralizing RHD care has the potential to bridge the aforementioned gaps and at least maintain or potentially increase, the uptake of secondary prophylaxis for RHD. A package of implementation strategies was developed with the aim of reducing barriers to optimum SAP uptake.

Methods and analysis: A hybrid implementation-effectiveness study type III was designed to evaluate the effectiveness of a package of implementation strategies that includes a mobile, cloud-based application to support decentralized RHD care, integrated into the public healthcare system in Uganda. Our overarching hypothesis is that secondary prophylaxis adherence can be maintained or improved via a decentralization strategy, compared to the centralized delivery strategy, by increasing retention in care. To evaluate this, patients currently cared for at the centralized RHD registry hospital sites will be consented for decentralized care at a health center located no more than 20 km from their home. The primary outcome will be adherence to secondary prophylaxis and detailed implementation measures will be collected to understand barriers and facilitators to decentralization, active community case management tool (ACT) application adoption, and ultimately its use and scale-up in the public healthcare system.

Ethics and dissemination: This study was approved by the Institutional Review Board (IRB) at Cincinnati Children's Hospital Medical Center, and Makerere University School of Medicine Research Ethics Committee (Mak-SOMREC). At completion, study findings will be published in peer-reviewed journals and communicated to the public and key stakeholders.

Keywords: Rheumatic Heart disease, BPG, Decentralization, Registry, Technology, Implementation science, Primary health center

Strengths and limitations of this study

- In this study, a potentially effective, scalable, sustainable approach to decentralization of RHD care for diagnosed patients is presented.
- The use of conventional study designs for establishing causality such as a cluster randomized control trial was limited by the number of people currently in RHD care in Uganda. However, the protocol outlines a practical, robust and iterative methodology which if successful, will inform future study designs to test the decentralization of interventions for chronic disease management in similar settings.
- The study demonstrates the feasibility of integrating an electronic registry for RHD patient management at the primary health care (PHC) level in a low-resource setting.

INTRODUCTION

Rheumatic Heart Disease (RHD) remains the most commonly acquired heart disease in people under 25 years of age (1). The median age at death, 28 years in Sub- Saharan Africa (2), translates into a large toll on the economically-productive age groups, resulting in rippled economic effects for already impoverished families (3). Furthermore, RHD is a disease associated with marked disparities, disproportionally affecting socioeconomically disadvantaged populations including children, women, poverty-stricken and marginalized minority ethnic groups (4–8). It is estimated that there are 39 million people with RHD globally, surpassing the number of people currently living with HIV/AIDS (4,9). Unlike HIV, which has seen sustained efforts towards control, RHD was not a priority on the international health development agenda for many years. Most low- income countries have no RHD programs in place, resulting in a gross underestimation of the prevalent cases and poor RHD knowledge by the healthcare workforce.

The first global resolution on rheumatic fever and RHD was adopted at the 71st World Health Assembly in 2018. Outlined among the broad clauses of this resolution is for countries to invest in community and primary healthcare workers as well as access to medicines for the prevention and control of RHD (10,11). Secondary antibiotic prophylaxis (SAP), in the form of monthly intramuscular Benzathine penicillin G (BPG), has been shown to be effective in preventing recurrent streptococcal infections - 'strep throat', acute rheumatic fever (ARF), and progression of RHD (12–14). However, these benefits are contingent on achieving an optimum adherence, at least $\geq$ 80% coverage of prescribed injections over many years of treatment (14,15). However, adherence is often suboptimal, leaving patients vulnerable to recurrent ARF and disease progression, a significant risk factor for death within eight months of diagnosis (16). Several factors have been shown to impact optimal BPG adherence – including drug supply shortages, distances travelled to the health facilities, and associated costs of attending hospitals for monthly injections (17–19).

Previous research in Uganda identified the distance people currently have to travel to receive routine monthly SAP is a major barrier, and a strong predictor of retention (20,21). This is due in part to the absent district-level RHD programs in Uganda, where primary health care (PHC) nurses do not have practical skills and tools to efficiently manage BPG delivery for RHD patients, despite the fact that this is well within their scope of practice. Moreover, registries have been identified as an important part of RHD control measures (22–24) and set forth as a priority by RHD experts (25).

However, in practice, centralized registries have often taken the form of static data collection (21), and not geared to scale to the community at large. While RHD programs are not yet operational at the district level in Uganda, we have an opportunity to improve access and uptake of BPG prophylaxis for the small fraction (1-2% of estimated total cases nationally) of people who have been identified and are active in the national RHD registry (20). Decentralization of care to primary health facilities has been employed for other diseases, the most widespread in the region being decentralization of HIV treatment to PHC nurses, allowing for major scale-up and availability of HIV services to those in-need (26).

Demonstrating that a modern approach to RHD care is effective and implementable is important because these tools will be critical to scaling RHD services to larger populations, as the capacity for the current centralized approach will be insufficient to serve the approximately 200 - 400 thousand persons estimated to be living with RHD in Uganda. Thus, there is a need to bring RHD care into the digital age, where technology-enhanced dynamic tools can be employed to improve RHD care delivery. The ADD-RHD (Active Case Detection and Decentralized Dynamic Registry to Improve the Uptake of Rheumatic Heart Disease Secondary Prevention) study was designed to address the above-mentioned challenges, including long distances to regional hospitals and the lack of a dynamic record system. The study is called "ADD-RHD" in part because the study "adds" RHD care to the list of competencies of PHC nurses in the study sites. As a major component of this study, the Active community case management tool (ACT) that was recently developed and piloted will be introduced in this setting, intended to support clinicians with technology-enhanced support tools (27).

Aims and hypothesis

This study aims to evaluate the effectiveness of a package of implementation strategies that include readiness assessment, change of service sites, change of records- keeping, health care worker training, purposefully re-examination of the implementation, identification of champions and physical supply of medicines for improving SAP delivery for RHD care. We hypothesize that this ADD-RHD package is equivalent or better than the existing model of care for SAP adherence.

METHODS AND ANALYSIS

Study design

This is a hybrid type III effectiveness-implementation study, that will be integrated into rural and semi-urban primary health centers. This design primarily focuses on the effectiveness of a package of implementation strategies whilst collecting secondary data on clinical outcomes (28). Decentralization of SAP delivery is postulated to at least preserve the level of adherence, whilst building capacity to scale up service delivery. The primary implementation endpoints will look at the post-implementation healthcare utilization outcomes among registrants, with a particular focus on SAP adherence (defined as proportion of days covered), which is strongly associated with the clinical outcomes of recurrence of ARF and progression of disease (14). The study will determine whether adherence to SAP is non-inferior post-implementation. Further, we will evaluate the acceptability, penetration, adoption, and cost of the implementation.

For secondary clinical outcomes, we will explore the relationship between program and adverse cardiovascular events (recurrent ARF, new or worsening heart failure, atrial fibrillation) and mortality compared to the baseline period. Because of the relatively small number of identified people with RHD in Uganda, and the centralized nature of secondary prophylaxis delivery currently at a small number of referral hospitals, the use of conventional implementation designs such as a cluster randomized control trial or interrupted series design was not possible. Instead, we developed

a non-randomized experiment using pre/post methods to demonstrate the impact of a package of strategies on implementation outcomes as well as intermediate clinical outcomes.

Study setting

Current RHD care provision – National registry at central and referral regional hospitals

Presently, a national RHD registry in Uganda is run centrally by research staff at the Uganda Heart Institute. Initially established in 2010, the registry subsequent expanded to include a satellite center in Kampala (Lebow) - and regional registry sites within 3 districts across the country (Mbarara, Gulu and Lira). The current RHD registry-based care in Uganda was initiated to capture people presenting with RHD to tertiary care and has served to establish numbers of those affected together with informing patient status. Dedicated research staff provide, coordinate and monitor routine BPG prophylaxis and RHD-related patient care in the country. The RHD registry is hosted electronically on REDCap, and involves both direct data entry and transfer of paper records into REDCap (29,30). However, the majority of records are paper-based and limited to the centers, which has proven to be outdated and ineffective (Table 1).

The new approach – ADD-RHD

Existing RHD registrants based in Lira and Gulu districts will have their monthly SAP visits decentralized from the current research-nurse led regional hospitals to outpatient settings of selected PHCs staffed by ministry of health nurses (Table 1). In this study, decentralization is defined as the physical change of service delivery of SAP for RHD registry patients from current regional hospitals to district level PHC facilities. As part of the ADD-RHD package, the ACT application will be introduced.

The Intervention

Our evidenced-based intervention, secondary antibiotic prophylaxis, has been previously proven to be effective in reducing the recurrence of strep throat and acute rheumatic fever, the cascade of events that can progress to RHD (14,15,31). In addition to reducing the progression of RHD, there is evidence that SAP can also induce the regression of clinical RHD (32). Unless contraindicated, BPG is the gold standard and most widely used for RHD secondary prevention (14).

In preparation for the study, facility visits, engagement of local and district health officers and consideration of the existing registry were done in order to inform important aspects of the implementation strategy (Figure 1).

RHD registry cleaning and collection of baseline data prior to decentralization

Prior to the study, existing RHD registrants were mapped by residence, and consequently, four HC III/IVs were chosen in each district based on diversity of location (city and rural parts of the districts) and RHD registrant geographical density (Figure 2). This was done in coordination with the local government, involving the District Health Administrator.

Initial collection of 12 – 18 months of intensive baseline data of existing RHD registry patients will be done for the two registry sites. Where necessary, patients will be contacted by phone for confirmation and completeness of information in order to determine baseline BPG adherence and retention data prior to decentralization. This data will be collected on a quarterly basis for important primary and secondary metrics defined.

Decentralization will be a phased process starting with two of the four clinics in Lira district, followed by the remaining two, with an approximate four-week gap in-between (Figure 1). Thereafter, this will be replicated in Gulu after a period of three months to allow incorporation of planned formative feedback from decentralization in the Lira district.

In this study, a package of implementation strategies (Table 2) will be employed to support a decentralized SAP delivery strategy to HC III/IV. This will be centered around the introduction of the ACT application further elaborated below.

ACT application

The ACT application is a digital tool-kit designed to build on REDCap, the current research database. The application incorporates several important features for RHD control including; 1) Availability of a simplified, interactive record of patients' administered BPG injections with automatic adherence calculations and relevant patient details, investigations and management; 2) A 'manage my patient' feature that allows clinicians to track patient status by due or missed visits that integrates with a clinician-facing reminder function, and 3) Monitoring of medicinal and supply stocks at facility and central levels. ACT is a small-scale medical record application built with the overarching goal of its integration for RHD care nationally and internationally, with potential to be replicated for use in other chronic disease management. Table 1 summarizes the current and new approach with regards to ACT as a novel electronic tool. Initial on-going site support visits have been planned at pre-determined intervals (frequently at first and then more spaced out) and will serve to provide refresher training on RHD and ACT. Data will be collected around these and incorporated into the implementation evaluation.

Provider education

Training of health workers from health centers will be central to this project. Whilst advocacy and awareness of RHD has been increasing overtime due to established research efforts, a large gap remains in provider RHD competency. Recent research found that less than 25% of facilities across several Ugandan districts had received any RHD training in the past two years and only 11% and 8% HC III and IVs had any RHD guidelines (34). Further, limited RHD knowledge was a prominent theme from published provider health care interviews, who expressed a strong desire for training (34).

Currently, service provision of BPG for RHD in HC III/IV is not done systematically. This informed an initial pilot training of representatives from each of the selected HCIII/IV facilities for decentralization in Lira. The pilot identified deficiencies in specific areas that was instrumental in tailoring educational materials developed for pre-decentralization training. We found variable but low RHD knowledge and experience among the HCWs. BPG is known to be a difficult injection to administer due to its nature to crystallize and presents challenges for unexperienced workers. A substantial portion of the planned training (and refresher sessions planned periodically thereafter), will focus on the practical aspects of BPG administration, as well as recognition and triage of potential BPG allergic reactions and anaphylaxis. The second set of training materials will consist of introduction to the ACT application. Furthermore, we developed a standard operating procedure (SOP), which will serve as the guideline for all decentralization procedures in health facilities in both districts.

'Champions', one of the implementation strategies, will be identified by the RHD research nurses based at the regional hospitals. The relationship between them and the staff at the health centers has been fostered overtime, giving them an advantage to identify motivated staff. In addition to this, the pilot training discussed above also contributed to the inclusion of medical records

representatives, who were not initially planned for. It was realized they are more technologically-competent and could provide IT support at the centers throughout the implementation.

Study population and recruitment

All eligible RHD registrants will be approached by trained study staff, the study explained and thereafter registrants will be invited to participate in decentralization. Registrants will be presented with the option to receive their care at one of the four community HCs selected in each district that is closest to them. Participation for all participants is voluntary and informed consent or assent from a parent or guardian (for those > 8 but < 18 years) will be sought and signed before enrolment.

Participant eligibility

Inclusion criteria. Eligible participants for decentralization will be all RHD registrants who live within 20 km of a participating health center.

Exclusion criteria. Registrants will be ineligible for participation if they have severe RHD - shown to be associated with an increased risk of a vasovagal mediated sudden deterioration during or immediately after a BPG injection; caution has been issued on BPG use in this population (35). According to these recommendations, we will exclude patients with severe mitral stenosis, severe aortic regurgitation or stenosis, ventricular dysfunction (EF < 50%) or with advanced symptoms (NYHA class III/IV) (35) as ascertained by echocardiography performed within 6 months prior to decentralization.

Registrants consenting to decentralization will have the necessary information regarding their care at HCs given to them during their last visit at the regional hospital, after which successive registration of health center nurses to the ACT application will commence. Given the novelty of systematic RHD SAP delivery in clinics, the research team will be on-site (at the health centers) for the first week and frequently thereafter, according to a documented schedule in order to provide the necessary support during this period. This will be phased out slowly over three to six months. As one of the key implementation strategies, we purposefully planned to re-examine implementation activities- including patient flow at clinics and the use of ACT for patient management. Any challenges identified will be attended to through a feedback process between healthcare workers in health centers, the research team and study administrators.

Implementation outcomes

For the primary implementation outcome, BPG adherence will be measured as a proxy for post-implementation healthcare utilization among registrants. The annualized proportion of persons who have ≥ 80% of days covered pre- and post-decentralization will be compared. At the individual level, adherence is calculated as the proportion of days covered over days prescribed BPG (Table 3). Data will be obtained from the ACT application and RHD REDCap registry for baseline pre-decentralization adherence data. Based on our hypothesis, we will be testing for non-inferiority of SAP adherence, post-implementation.

The taxonomy of implementation constructs proposed by Proctor et al. (36) will be used to guide the data collection, levels of analysis, and measurement of implementation outcomes, with particular emphasis on acceptability, adoption, penetration, and implementation cost.

Pre-implementation, formative research was planned among stakeholders in the two districts to ensure ADD-RHD is suitable and feasible. Facility surveys will collect monthly data on clinic staff numbers and roles, availability of drugs (which will inform drug-stock outs) and consumables - with

particular emphasis on RHD care-relevant supplies. We will evaluate the implementation outcomes of acceptability, adoption and penetration by conducting a concurrent mixed methods evaluation of the ADD-RHD program (Table 4). Pre/post decentralization patient and provider qualitative interviews using semi-structured questionnaires have been planned within a month prior to decentralization to get in-depths perspectives from potential participants, including foreseen barriers to program roll-out. This was intended to be formative, and no formal framework will be used. However, six key areas of interest pertaining to decentralization were used to develop *a priori* data extraction template. A matrix-based rapid qualitative analysis will be done and themes and sub-themes generated will enable the incorporation of findings in real-time to optimize the decentralization of RHD care. This was planned as part of implementation iteration (together with a staggered roll-out in Lira and then Gulu district), for quality improvement.

Database queries, anecdotes, user inquiries and field diaries from support staff will be kept to inform challenges and successes of implementation. In particular, we will collect data on patient use of health centers and return rates (if any) to the regional hospital that will inform acceptability (Table 4). A sub-study will evaluate costs, as an important implementation outcome. High out of pocket (OOP) costs have been previously documented to be associated with the current centralized care (3). It is postulated that a decentralized model will result in reduction of OOP expenditures. To enable this evaluation, pre-planned patient surveys, time and motion studies and facility cost data will be used in an embedded economic evaluation and reported separately from the main study. Furthermore, time and motion studies will be incorporated to evaluate any disruptions to care and potential distribution of valuable manpower resources which will be valuable for planning and scaling the intervention if it were successful.

Secondary clinical outcomes

Information on secondary clinical outcomes will be reported (Table 3). We will assess the non-inferiority of the decentralized registry on rates of retention at two years post implementation (Table 3). Further, a composite of adverse cardiovascular events, including a combination of new or worsening heart failure, recurrent ARF, atrial fibrillation, infective endocarditis and mortality will be documented during decentralization and records extracted for baseline period rates. In an exploratory analysis, using continuous measures of adherence, we will compare event rates among more- and less-adherent participants to validate the purported dose-response relationship between SAP and ARF, clinical progression of RHD in this context.

Statistical considerations

The primary outcome of the study is to determine whether adherence after decentralization is non-inferior to the baseline adherence recorded for national RHD registry. We propose a one-sided exact binomial test at alpha = 0.025 of the null hypothesis that the proportion of adherent patients during the intervention period is less than baseline by more than 10%. Based on previous experience with this patient population, we expect approximately 150 - 200 persons with RHD will contribute data on adherence during the baseline and intervention periods in Lira and Gulu. We also approximate 75% of these patients will receive 80% of BPG injections. Table 4 provides the expected power (1 – beta) for plausible values of the sample size (n), baseline percent adherent (BPA), and non-inferiority margin. Based on these assumptions, for alpha = 0.025 (one-sided) taking a total of between 150 - 200 participants will provide between 72 - 86% power to reject the null hypothesis of inferiority when the baseline percent adherent is 75% and the NIM is -10%. Thus, we expect to be at least moderately powered to reject the null hypothesis of inferiority at the proposed non-inferiority margin.

DISCUSSION

Like many chronic diseases, the successful prevention of RHD entails optimum adherence to monthly BPG injections, the cornerstone of RHD control. Decentralization of health services has long been advocated as a means to improve health service delivery and reach (37). Successful decentralization of care to PHCs resulted in the widespread availability and accessibility of HIV treatments in similar settings, playing a key role in HIV program successes (38). Disease registries have been previously advocated in the early 2000s by organizations such as World Health Federation and RHD Action (39), which outlined minimum standards and guidance for RHD registries. However, these efforts have seen variable country uptake, often characterized by centralized registries, fragile paper records and limitations in quality assurance and continuous monitoring. To date, no modern version of a decentralized national RHD registry currently exists in LMICs. The ACT application, one of the packages of implementation strategies, was designed to mitigate the static nature of registries and further aid health workers in managing RHD secondary prevention. If successful, this will modernize how we approach RHD secondary prevention in Uganda and other similar settings, where RHD is prevalent. Based on this, and through long-standing partnerships encompassing local, regional and district key stakeholder engagement, we established the feasibility and suitability of ADD-RHD.

ACT is a novel technology-enabled dynamic application that integrates features to empower health workers at all levels of care with supportive tools to track, monitor and better engage RHD patients. In addition, the application will facilitate health center communication channels to responsible bodies, such as relevant persons in medical supplies and the ministry of health, an important aspect to ensure availability of medicines, supplies and quality improvement. Electronic medical records are yet to be incorporated widely in health facilities in Uganda, hence the tailored simplification for PHCs and initial support provided by the current research collaborative will be valuable and presents a potential for its absorption into future EMR expansion plans (27). Ultimately, the study can be used as a model for chronic disease management by informing how we integrate these digital health systems to enhance patient care in similar settings where HCWs are not necessarily well-versed with computers or technology.

We acknowledge some limitations to this study. Firstly, the study design was not according to conventional methods for establishing causality for the reasons previously mentioned. We acknowledge the fixed sample size, reflecting the limited cases currently identified and established in the registry from previous screening efforts. The use of fairly robust and more comprehensive mixed-methods with the additional collection of more granular data was designed to mitigate some of these limitations. Another potential limitation is around the ACT application, requiring baseline user comfort with technology and smart phones, which was not the case with some community public health workers. The pilot training informed the development of a simplified application version tailored specifically to the roles of the HCWs (27). In addition, internet connectivity is often unstable is this setting, which informed the incorporation of an offline feature function that may enhance the functionality and uptake of the application. Lastly, several other system-level factors pose potential challenges, including long waiting times, staff shortages and drug availability that are generalizable country-wide, but which may impact implementation. Securing medication by use of external resources in the initial period limits the generalizability without modifications to the health system. However, it demonstrates the values of securing supplies to make improvements and signifies more work needs to be done in this area. Ultimately, through the project, there is an opportunity to re-design and equip PHCs to overcome some of these barriers to healthcare and serve as a foundation for scaling up much needed RHD services to different parts of the country.

CONCLUSION

Rheumatic heart disease is attributed to a large burden of premature cardiovascular morbidity and mortality in endemic countries. Despite evidence regarding SAP, endemic areas are defined by poor health-seeking behavior, limited access to healthcare, and challenges around centralized and static registries. This study was designed to address previous obstacles documented in the country - highlighting barriers to life-saving secondary prevention. Overall, the successful implementation of the study and hence availability of service at PHCs closer to registrants' residences may benefit the country at large given the potential it presents for scaling up RHD care in other districts. We believe the current relationships fostered over years with regional registry sites, local government and national government will serve as a stepping stone for successful decentralization, increasing access to BPG prophylaxis and working towards achieving the control of rheumatic heart disease countrywide.

Word count: 3975

Study Status

The ADD-RHD study was initially approved on 04/03/2021. Decentralization of study participants is currently being finalized in the second site and post-decentralization data collection will follow for 12 months to December 2023. Data analysis is planned to start early 2024, with the full project due for completion in April 2024.

LIST 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
ARF: Acute Rheumatic Fever
BPG: Benzathine Penicillin G
EMR: Electronic Medical Records
HC III/IV: Health Center III/IV
HCW: health Care Worker
LMIC: Low- and middle Income country
MOH: Ministry of Health
OOP: Out of Pocket
PHC: Primary Health Care
RHD: Rheumatic Heart Disease
SAP: Secondary Antibiotic Prophylaxis

DECLARATIONS

Ethics approval and consent to participate

This protocol was reviewed and approved by the Institutional Review Board (IRB) at Cincinnati Children's Hospital Medical Center, and Makerere University School of Medicine Research Ethics Committee (Mak-SOMREC-2021-61).

Consent for publication

Not applicable

Availability of data and materials
Data collection instruments are available on request as supplementary documents

Competing interests
The authors declare that they have no competing interests

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Author Contributions
AB, DW, EO, CL, CS, JR and KD initially conceptualized the different aspects of the study. DW, KD, AB, NM, JP, JR, EO, NO, JD, SdL, RS, NF and JA contributed to the study design and proposal. NM, JP, JR, NF, SdL, RS, JA, JK, DN, LM, FO, HN, YS, KD, & DW contributed to the implementation aspects of the study. NM, DW, AB, KD wrote the initial draft of the protocol paper. All authors reviewed, updated and approved the final protocol.

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LIST OF TABLES

Table 1. Comparison of current and proposed SAP delivery approaches

	Current Approach – National RHD Registry	**Proposed approach – Decentralized RHD Registry at district level health facilities**
Location	Limited to central and regional referral centers	Expansion to Health center III/IV (Lira and Gulu districts)
Staff	Dedicated research staff regionally	This approach will incorporate existing MOH staff at HCIII/IV at district and regional hospitals, as well as administrators and different stakeholders from Ministerial representatives
Patient records and data	REDCap/paper-based clinical records • Web-based electronic database largely supporting research activities • A mix of direct entry and transfer of paper records have been used. • Not scalable; not enabled to support clinical management.	ACT application • Keeps track of BPG injections • Automatic adherence calculation • Intended for direct entry by HCWs • Managing patient features categorized for 'due' and 'missed' injections • Iterative – patient reminder integration and tracking; clinician/specialist/MOH representative communication features • Quality metrics - Allows easily generated quality reports for examining overall adherence, referrals for procedures and the ability to compare across facilities and regions. Potentially scalable nationwide for RHD and other chronic illnesses.
SAP, Secondary Antibiotic Prophylaxis; RHD, Rheumatic Heart Disease; HC III/IV, Health Center III/IV; MOH, Ministry of Health; ACT – Active Community Case Management Tool; HCW – Health Care Worker		

Table 2. ADD-RHD Implementation strategies mapped according to Expert Recommendations for Implementing Change (ERIC) discreet implementation strategies (33)

Strategy	Details
Assess for readiness and identify barriers and facilitators	Assessment for readiness will be done through facility visits, surveys, and engagement of local and district health officers (DHO). Patient and provider interviews will identify barriers and facilitators to decentralization. Key stakeholder and community engagement on decentralization logistics will serve to establish key components of the process.
Change of service sites (decentralization)	Four health facilities were identified based on patient clusters and distances from their residences primarily geared at increasing access and reducing distances travelled.
Training Health Care workers (HCWs)/ develop educational materials	HCW training was planned to include the development of education materials on RHD clinical knowledge, BPG preparation and injection skills, penicillin adverse events recognition and first aid management. A detailed description is provided below.
Change record systems	ACT application was specifically developed as a clinical tool for HCWs through stakeholder engagement and piloting (27). It encompasses in-built tools to enhance patient engagement, including clinicians' monitoring of adherence and quality metrics for monitoring supply stocks. This will replace the current regional registry. A detailed description is provided below.
Purposefully re-examine the implementation	We built in milestones to re-examine implementation activities, identify challenges, and provide feedback and support to health facilities in order to continuously improve the quality of care. This includes looking at the use of ACT for patient management, identifying challenges and giving feedback to healthcare workers in health centers.
Identify and prepare champions	Initial assessment for readiness informed the need for local champions at each health center, selected to drive the implementation by providing support and driving quality improvement activities such as updating stock and supplies data for quality metrics on the ACT application.
Physical supply of medicines*	Although historically used to treat other conditions, such as syphilis, its consistent availability is variable in public facilities in Uganda. Hence, through stakeholder and local engagement, temporary BPG supply was found to be an essential initial component to the success of the intervention at a few facilities. This marked an iterative adaptation in light of short-term regulatory constraints. For some facilities, increasing BPG supply through the government system was motivated by history of use, and hence a gap in supply was inevitable during the initial post-decentralization period. Covering this gap was an important aspect to implementation.
*Not a specific ERIC implementation strategy. DHO, District Health Officer; HCW, Health Care Worker; RHD, Rheumatic Heart Disease; ACT, Active Community Case Management Tool; BPG, Benzathine Penicillin G	

Table 3. Key metrics collected during baseline data collection

Primary Metric	Operational Definition	Collection Method
BPG Adherence	The proportion of persons who have 80% of days covered. Each registrants' days of coverage will be calculated as: Days of coverage (%) = Days with adequate BPG coverage*/Days prescribed BPG. *Adequate BPG coverage defined as the prescribed interval between BPG injection (i.e. 28, 21, or 14 days).	National Registry and ACT application, based on dates of injections as compared to prescription
Secondary Metrics	**Operational Definition**	**Collection Method**
Retention	Defined as being seen at least twice in a 12-month period for clinical review (outside or in conjunction with BPG delivery)	National Registry and ACT application
Composite Adverse CV events	Combination of new or worsening heart failure, atrial fibrillation, infective endocarditis, and/or recurrent ARF	National Registry and ACT application, supplemented as needed by patient interview
RHD Mortality	Death of an RHD registrant that is determined to be the direct or indirect result of RHD.	Multimodality, direct report from family or hospital/clinic if death was witnessed by medical staff
BPG Stockouts	# days with no BPG or BPG-related supplies (needles, syringes, dilutant, lidocaine, etc.) to be tracked individually, and # of days at <20% supply (based on anticipated number of RHD registrants assigned to that clinical location)	ONLY tracked during decentralized care, through both stock inventory by our research staff (monthly surveillance) and reports on the ACT application
BPG, Benzathine Penicillin G; ACT, Active Community Case Management Tool; CV, cardiovascular; RHD, Rheumatic Heart Disease		

Table 4. Data sources for the evaluation of implementation outcomes

	Provider Level	Patient Level	Facility Level	ACT Application Audits	Record Audit at RRH Visits
Acceptability	Provider pre-/post-decentralization interviews	Patient pre-/post-decentralization interviews Coded under acceptability and Health setting preferences	Administrator interview	ACT usage audit/data queries Documented ACT application changes	RRH injection record audits; Self-decentralization rates and rates of return to RRH post-decentralization
Adoption	Provider pre-/post-decentralization interviews. Observation Time & Motion study	N/A	Monthly Health facility survey - organization & appropriateness of RHD medicinal and supplies order based on need. Direct observation	Provider pre-/post-decentralization interviews. ACT usage audit; -Trends of use by HC nurses -Completeness of BPG injections -Use of additional features (Reminder & Update of stock alerts)	Examination of entered data on BPG card versus ACT application
Penetration	Provider pre-/post-decentralization interviews. Attendance to RHD cases. Numbers of providers trained versus numbers delivering service	N/A	Monthly Health facility survey - Improvements in medicinal (BPG) and supply shortages Direct observation Regular attendance of RHD patients	Query-generation rates on ACT application Use of paper records for RHD care ACT usage by HC nurses – completion of information and other usage parameters overtime Rates of re-education for HC nurses on deficient areas identified	Reduction in BPG visits to RRH services for decentralized registrants

RRH, Regional referral hospital; ACT, Active community case management tool; HC, Health Center

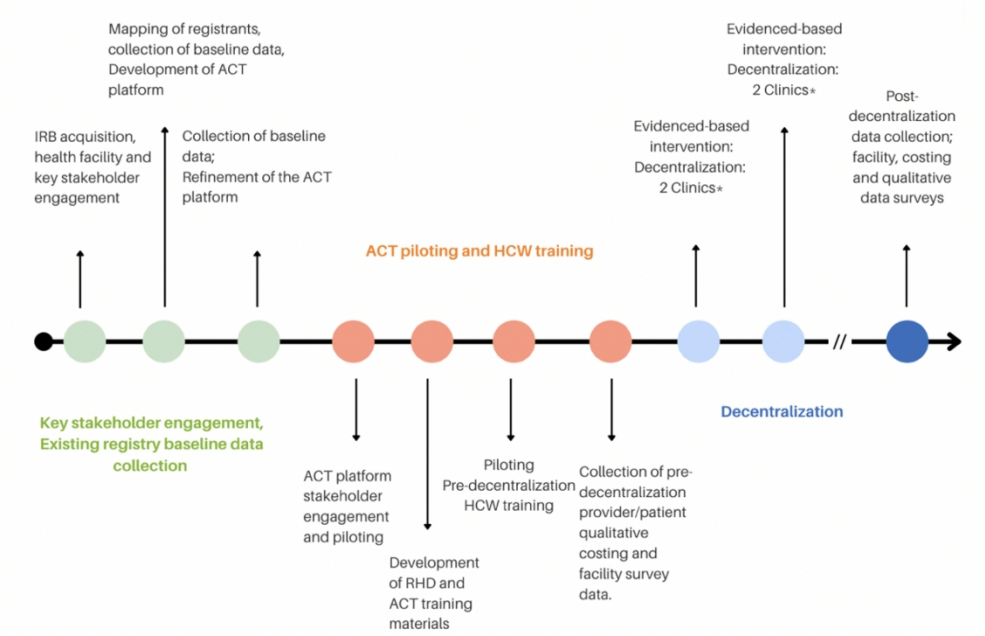

Figure 1. Sequential outline of ADD-RHD implementation plans for Lira. ADD-RHD, Active Case Detection and Decentralized Dynamic Registry to Improve the Uptake of Rheumatic Heart Disease Secondary Prevention; ACT, Active Community Case Management Tool; IRB, Institutional Review Board; HCW, Health Care Worker

576x389mm (57 x 57 DPI)

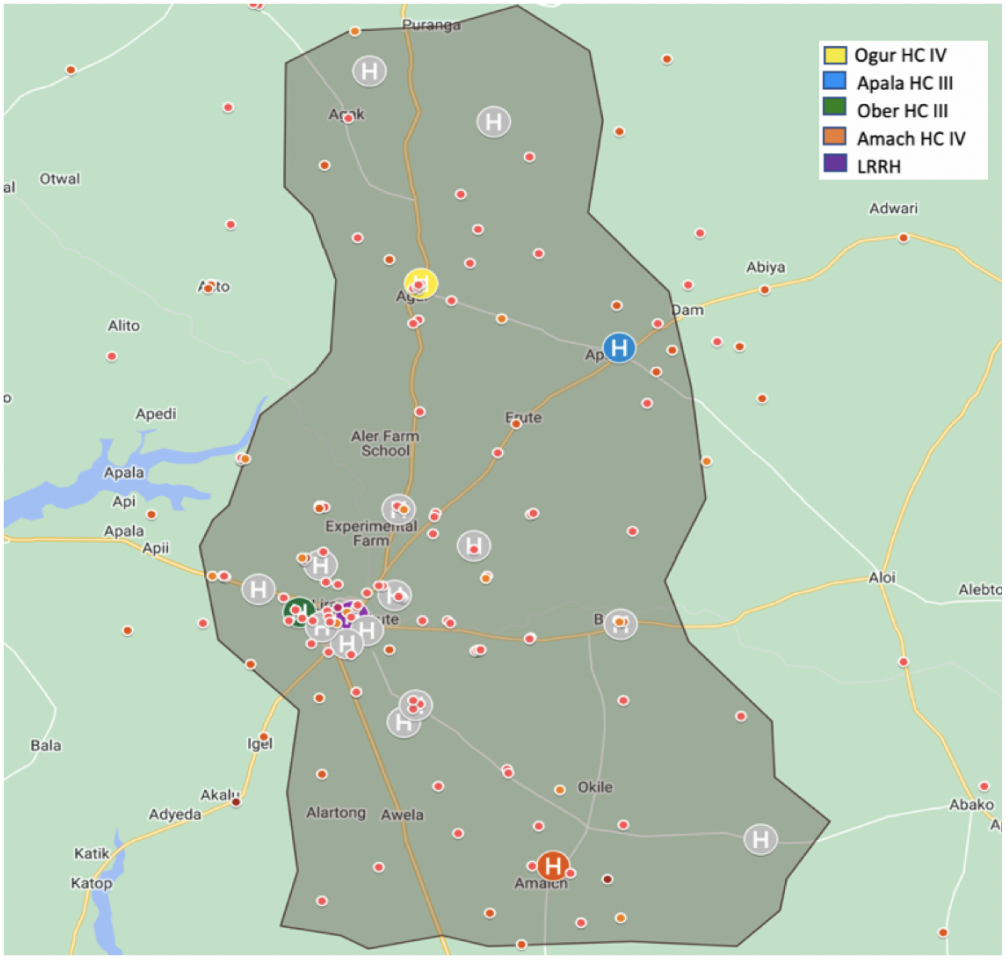

Figure 2. The four selected health centers in Lira according to RHD registrants' geographical density. Identified health centers are HCIV (Ogur, Amach) and HC III (Ober and Apala). LRRH, Lira Regional Referral Hospital; HC, Health Centre

507x483mm (57 x 57 DPI)

Standards for Reporting Implementation Studies: the StaRI checklist for completion

The StaRI standard should be referenced as: Pinnock H, Barwick M, Carpenter C, Eldridge S, Grandes G, Griffiths CJ, Rycroft-Malone J, Meissner P, Murray E, Patel A, Sheikh A, Taylor SJC for the StaRI Group. Standards for Reporting Implementation Studies (StaRI) statement. *BMJ* 2017;356:i6795

The detailed Explanation and Elaboration document, which provides the rationale and exemplar text for all these items is: Pinnock H, Barwick M, Carpenter C, Eldridge S, Grandes G, Griffiths C, Rycroft-Malone J, Meissner P, Murray E, Patel A, Sheikh A, Taylor S, for the StaRI group. Standards for Reporting Implementation Studies (StaRI). Explanation and Elaboration document. *BMJ Open* 2017 2017;7:e013318

Notes: A key concept of the StaRI standards is the dual strands of describing, on the one hand, the implementation strategy and, on the other, the clinical, healthcare, or public health intervention that is being implemented. These strands are represented as two columns in the checklist.

The primary focus of implementation science is the implementation strategy (column 1) and the expectation is that this will always be completed.	The evidence about the impact of the intervention on the targeted population should always be considered (column 2) and either health outcomes reported or robust evidence cited to support a known beneficial effect of the intervention on the health of individuals or populations.

The StaRI standardsrefers to the broad range of study designs employed in implementation science. Authors should refer to other reporting standards for advice on reporting specific methodological features. Conversely, whilst all items are worthy of consideration, not all items will be applicable to, or feasible within every study.

Checklist item		Reported on page #	Implementation Strategy	Reported on page #	Intervention
			"Implementation strategy" refers to how the intervention was implemented		"Intervention" refers to the healthcare or public health intervention that is being implemented.
Title and abstract					
Title	**1**	1	Identification as an implementation study, and description of the methodology in the title and/or keywords		
Abstract	**2**	1	Identification as an implementation study, including a description of the implementation strategy to be tested, the evidence-based intervention being implemented, and defining the key implementation and health outcomes.		
Introduction					
Introduction	**3**	2	Description of the problem, challenge or deficiency in healthcare or public health that the intervention being implemented aims to address.		
Rationale	**4**	3	The scientific background and rationale for the implementation strategy (including any underpinning theory/framework/model, how it is expected to achieve its effects and any pilot work).	3, 5	The scientific background and rationale for the intervention being implemented (including evidence about its effectiveness and how it is expected to achieve its effects).

Aims and objectives	**5**	3	The aims of the study, differentiating between implementation objectives and any intervention objectives.		
Methods: description					
Design	**6**	3	The design and key features of the evaluation, (cross referencing to any appropriate methodology reporting standards) and any changes to study protocol, with reasons		
Context	**7**	4, 5	The context in which the intervention was implemented. (Consider social, economic, policy, healthcare, organisational barriers and facilitators that might influence implementation elsewhere).		
Targeted 'sites'	**8**	4, 6	The characteristics of the targeted 'site(s)' (e.g. locations/personnel/resources etc.) for implementation and any eligibility criteria.	8	The population targeted by the intervention and any eligibility criteria.
Description	**9**	6 - 8	A description of the implementation strategy	5	A description of the intervention
Sub-groups	**10**	NA	Any sub-groups recruited for additional research tasks, and/or nested studies are described		
Methods: evaluation					
Outcomes	**11**	9-11	Defined pre-specified primary and other outcome(s) of the implementation strategy, and how they were assessed. Document any pre-determined targets	9-11	Defined pre-specified primary and other outcome(s) of the intervention (if assessed), and how they were assessed. Document any pre-determined targets
Process evaluation	**12**	10	Process evaluation objectives and outcomes related to the mechanism by which the strategy is expected to work		
Economic evaluation	**13**	*	Methods for resource use, costs, economic outcomes and analysis for the implementation strategy	*	Methods for resource use, costs, economic outcomes and analysis for the intervention
Sample size	**14**	11	Rationale for sample sizes (including sample size calculations, budgetary constraints, practical considerations, data saturation, as appropriate)		
Analysis	**15**	11	Methods of analysis (with reasons for that choice)		
Sub-group analyses	**16**	10	Any a priori sub-group analyses (e.g. between different sites in a multicentre study, different clinical or demographic populations), and sub-groups recruited to specific nested research tasks		

Results					
Characteristics	**17**	N/A	Proportion recruited and characteristics of the recipient population for the implementation strategy	N/A	Proportion recruited and characteristics (if appropriate) of the recipient population for the intervention
Outcomes	**18**	N/A	Primary and other outcome(s) of the implementation strategy	N/A	Primary and other outcome(s) of the Intervention (if assessed)
Process outcomes	**19**	N/A	Process data related to the implementation strategy mapped to the mechanism by which the strategy is expected to work		
Economic evaluation	**20**	N/A	Resource use, costs, economic outcomes and analysis for the implementation strategy	N/A	Resource use, costs, economic outcomes and analysis for the intervention
Sub-group analyses	**21**	N/A	Representativeness and outcomes of subgroups including those recruited to specific research tasks		
Fidelity/ adaptation	**22**	N/A	Fidelity to implementation strategy as planned and adaptation to suit context and preferences	N/A	Fidelity to delivering the core components of intervention (where measured)
Contextual changes	**23**	N/A	Contextual changes (if any) which may have affected outcomes		
Harms	**24**	N/A	All important harms or unintended effects in each group		
Discussion					
Structured discussion	**25**	12	Summary of findings, strengths and limitations, comparisons with other studies, conclusions and implications		
Implications	**26**	12	Discussion of policy, practice and/or research implications of the implementation strategy (specifically including scalability)	12	Discussion of policy, practice and/or research implications of the intervention (specifically including sustainability)
General					
Statements	**27**	13 - 14	Include statement(s) on regulatory approvals (including, as appropriate, ethical approval, confidential use of routine data, governance approval), trial/study registration (availability of protocol), funding and conflicts of interest		

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Evaluating the implementation of a dynamic digital application to enable community-based decentralization of rheumatic heart disease case management in Uganda: A hybrid type III effectiveness-implementation study protocol

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Evaluating the implementation of a dynamic digital application to enable community-based decentralization of rheumatic heart disease case management in Uganda: A hybrid type III effectiveness-implementation study protocol

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ABSTRACT:

Introduction: Rheumatic heart disease (RHD) affects over 39 million people worldwide, the majority in low- and middle- income countries. Secondary antibiotic prophylaxis (SAP), given every 3 to 4 weeks can improve outcomes, provided more than 80% of doses are received. Poor adherence is strongly correlated with the distance travelled to receive prophylaxis. Decentralizing RHD care has the potential to bridge these gaps and at least maintain or potentially increase RHD prophylaxis uptake. A package of implementation strategies was developed with the aim of reducing barriers to optimum SAP uptake.

Methods and analysis: A hybrid implementation-effectiveness study type III was designed to evaluate the effectiveness of a package of implementation strategies including a digital, cloud-based application to support decentralized RHD care, integrated into the public healthcare system in Uganda. Our overarching hypothesis is that secondary prophylaxis adherence can be maintained or improved via a decentralization strategy, compared to the centralized delivery strategy, by increasing retention in care. To evaluate this, eligible RHD patients irrespective of their age enrolled at Lira and Gulu hospital registry sites will be consented for decentralized care at their nearest participating health centre. We estimated a sample size of 150-200 registrants. The primary outcome will be adherence to secondary prophylaxis whilst detailed implementation measures will be collected to understand barriers and facilitators to decentralization, digital application tool adoption, and ultimately its use and scale-up in the public healthcare system.

Ethics and dissemination: This study was approved by the Institutional Review Board (IRB) at Cincinnati Children's Hospital Medical Center (IRB 2021-0160), and Makerere University School of Medicine Research Ethics Committee (Mak-SOMREC- 2021-61). Participation will be voluntary and informed consent or assent (>8 but <18) will be obtained prior to participation. At completion, study findings will be communicated to the public, key stakeholders and submitted for publication.

Keywords: Rheumatic Heart disease, BPG, Decentralization, Registries, Technology, Implementation science, Primary health centre

Strengths and limitations of this study

- The study methodology outlines an evaluation approach for decentralized care programs for Rheumatic Heart disease, which has not been described before, integrating an electronic RHD registry for primary health care
- A range of implementation strategies are incorporated within a robust and iterative methodology that address known barriers to care
- Two different geographical settings are used for the implementation in Uganda, increasing the external validity
- The study is limited by the pre/post design and lacks an external control group
- The small number of participating facilities and patients will limit understanding the effectiveness of the intervention.

INTRODUCTION

Rheumatic Heart Disease (RHD) remains the most commonly acquired heart disease in people under 25 years of age (1). The median age at death, 28 years in Sub- Saharan Africa (2), translates into a large toll on the economically-productive age groups, resulting in rippled economic effects for already impoverished families (3). Furthermore, RHD is a disease associated with marked disparities, disproportionally affecting socioeconomically disadvantaged populations including children, women, poverty-stricken and marginalized minority ethnic groups (4–8). It is estimated that there are 39 million people with RHD globally, surpassing the number of people currently living with HIV/AIDS (4,9). Unlike HIV, which has seen sustained efforts towards control, RHD was not a priority on the international health development agenda for many years. Most low- income countries have no RHD programs in place, resulting in a gross underestimation of the prevalent cases and poor RHD knowledge among the healthcare workforce.

The first global resolution on rheumatic fever and RHD was adopted at the 71st World Health Assembly in 2018. Outlined among the broad clauses of this resolution is for countries to invest in community and primary healthcare workers as well as access to medicines for the prevention and control of RHD (10,11). Secondary antibiotic prophylaxis (SAP), in the form of monthly intramuscular Benzathine penicillin G (BPG), has been shown to be effective in preventing recurrent streptococcal infections - 'strep throat', acute rheumatic fever (ARF), and progression of RHD (12–14). These benefits are contingent on achieving an optimum adherence, at least $\geq$ 80% coverage of prescribed injections over many years of treatment (14,15). However, adherence is often suboptimal, leaving patients vulnerable to recurrent ARF and disease progression, a significant risk factor for death within eight months of diagnosis (16). Several factors have been shown to impact optimal BPG adherence – including drug supply shortages, distances travelled to the health facilities, and associated costs of attending hospitals for monthly injections (17–19).

Previous research in Uganda identified the distance people currently have to travel to receive routine monthly SAP is a major barrier, and a strong predictor of retention (20,21). This is due in part to the absent district-level RHD programs in Uganda, where primary health care (PHC) nurses do not

have practical skills and tools to efficiently manage BPG delivery for RHD patients, despite the fact that this is well within their scope of practice. Moreover, registries have been identified as an important part of RHD control measures (22–24) and set forth as a priority by RHD experts (25). In practice, centralized registries have often taken the form of static data collection (21), and not geared to scale to the community at large. While RHD programs are not yet operational at the district level in Uganda, we have an opportunity to improve access and uptake of BPG prophylaxis for the small fraction (1-2% of estimated total cases nationally) of people who have been identified and are active in the national RHD disease registry (20). Decentralization of care to primary health facilities has been employed for other diseases, the most widespread in the region being decentralization of HIV treatment to PHC nurses, allowing for major scale-up and availability of HIV services to those in-need (26).

Demonstrating that a new approach to RHD care is effective and implementable is important for scaling RHD services more broadly. The capacity within the current centralized approach is insufficient to serve the approximately 200 - 400 thousand persons estimated to be living with RHD in Uganda. Thus, there is a need to bring RHD care into the digital age, where technology-enhanced dynamic tools can be employed to improve RHD care delivery. The ADD-RHD (Active Case Detection and Decentralized Dynamic Registry to Improve the Uptake of Rheumatic Heart Disease Secondary Prevention) study was designed to address the above-mentioned challenges, including long distances to regional hospitals and the lack of a dynamic record system. The study is called "ADD-RHD" in part because the study "adds" RHD care to the list of competencies of PHC nurses in the study sites. As a major component of this study, the Active community case management tool (ACT) that was recently developed and piloted will be introduced in this setting, intended to support clinicians with technology-enhanced support tools (27).

Aims and hypothesis

This study aims to evaluate the effectiveness of a package of implementation strategies that includes: assessment of site readiness, decentralization of service sites, a new mode of electronic record- keeping, health care worker training, iterative feedback during implementation, identification of champions and physical supply of medicines for improving SAP delivery for RHD care. We hypothesize that this package of strategies will be equivalent to or improve the current SAP adherence and related outcomes for enrollees in the decentralized study locations.

METHODS AND ANALYSIS

Study design

This is a mixed methods, hybrid type III effectiveness-implementation study, that will be integrated into rural and semi-urban primary health centres. This design primarily focuses on the effectiveness of a package of implementation strategies whilst collecting secondary data on clinical outcomes (28). Decentralization of SAP delivery is postulated to at least preserve the level of adherence, whilst building capacity to scale up service delivery. The primary implementation endpoints will look at the post-implementation healthcare utilization outcomes among enrolled patients, with a particular focus on SAP adherence (defined as proportion of days covered), which is strongly associated with the clinical outcomes of recurrence of ARF and progression of disease (14). The study will determine whether adherence to SAP post-implementation is non-inferior to the current, centralized care. We estimated a total of 150 - 200 persons with RHD Lira and Gulu will be eligible for decentralization (statistical considerations below). Further, we will evaluate the acceptability, penetration, adoption, and cost of the implementation.

For secondary clinical outcomes, we will explore the relationship between program and adverse cardiovascular events (recurrent ARF, new or worsening heart failure, atrial fibrillation) and mortality compared to the baseline period. Because of the relatively small number of identified people with RHD in Uganda, and the centralized nature of secondary prophylaxis delivery currently at a small number of referral hospitals, we developed a non-randomized experiment using pre/post methods to demonstrate the impact of a package of strategies on implementation outcomes as well as intermediate clinical outcomes.

Study setting

Current RHD care provision – National registry at central and referral regional hospitals

Presently, a national RHD registry, a collection of clinical data for RHD patients enrolled and known to the healthcare system in Uganda is run centrally by research staff at the Uganda Heart Institute (Kamplala). Initially established in 2010, the registry subsequently expanded to include a satellite centre in Kampala (Lebowa) - and regional registry sites within 3 districts across the country (Mbarara, Gulu and Lira). The current RHD registry-based care in Uganda was initiated to capture people presenting with RHD to tertiary care and has served to establish numbers of those affected together with informing patient status. Dedicated research staff provide, coordinate and monitor routine BPG prophylaxis and RHD-related patient care in the country. The RHD registry is hosted electronically on REDCap, and involves both direct data entry and transfer of paper records into REDCap (29,30). However, the majority of records are paper-based and limited to the centres, which has proven to be outdated and ineffective (Table 1).

The new approach – ADD-RHD

Existing RHD registrants based in Lira and Gulu districts will have their monthly SAP visits decentralized from the current research-nurse led regional hospitals to outpatient settings of selected PHCs staffed by ministry of health nurses (Table 1). In this study, decentralization is defined as the change of service sites for delivery of SAP for RHD registry patients, from current regional hospitals to district level PHC facilities. As part of the ADD-RHD package, the ACT application (see below) will be introduced.

Table 1. Comparison of current and proposed SAP delivery approaches

	Current Approach – National RHD Registry	**Proposed approach – Decentralized RHD Registry at district level health facilities**
Location	Limited to central and regional referral centres	Expansion to Health centres III/IV (Lira and Gulu districts)
Staff	Dedicated research staff regionally	This approach will incorporate existing MOH staff at HCIII/IV at district and regional hospitals, as well as administrators and different stakeholders from Ministerial representatives
Patient records and data	REDCap/paper-based clinical records • Web-based electronic database largely supporting research activities	ACT application • Keeps track of BPG injections • Automatic adherence calculation • Intended for direct entry by HCWs

	• A mix of direct entry and transfer of paper records have been used. • Not scalable; not enabled to support clinical management.	• Managing patient features categorized for 'due' and 'missed' injections • Iterative – patient reminder integration and tracking; clinician/specialist/MOH representative communication features • Quality metrics - Allows easily generated quality reports for examining overall adherence, referrals for procedures and the ability to compare across facilities and regions. Potentially scalable nationwide for RHD and other chronic illnesses.
SAP, Secondary Antibiotic Prophylaxis; RHD, Rheumatic Heart Disease; HC III/IV, Health Centre III/IV; MOH, Ministry of Health; ACT – Active Community Case Management Tool; HCW – Health Care Worker		

The Intervention

The evidenced-based practice, secondary antibiotic prophylaxis, has been proven to be effective in reducing the recurrence of strep throat and acute rheumatic fever, the cascade of events that can progress to RHD (14,15,31). In addition to reducing the progression of RHD, there is evidence that SAP can also induce the regression of clinical RHD (32). Unless contraindicated, BPG is the gold standard and most widely used for RHD secondary prevention (14).

Preparation for decentralization

In preparation for the study, facility visits, engagement of local and district health officers and consideration of the existing registry were done in order to inform important aspects of the implementation strategy.

Existing RHD registrants were mapped by residence, and consequently, four level 3 and 4 health centres (HCIII/IV) were chosen in each district based on diversity of location (city and rural parts of the districts) and RHD registrant geographical density (Figure 1). This was done in coordination with the local government, involving the District Health Administrator. In Uganda, rural and semi-urban areas are served by primary care health facilities with designated levels 1 – 4, where level 1 is the lowest basic dispensary and 4 with more services such as maternity care.

Initial collection of 12 – 18 months of intensive baseline data of existing RHD registry patients will be done at the Lira and Gulu regional hospitals, where RHD patient care is currently based. Where necessary, patients will be contacted by phone for confirmation and completeness of information in order to determine baseline BPG adherence and retention data prior to decentralization. This data will be collected on a quarterly basis for important primary and secondary metrics defined.

Decentralization will be a phased process starting with two of the four clinics in Lira district, followed by the remaining two, with an approximate four-week gap in-between. Thereafter, this will be replicated in Gulu after a period of four – six months to allow incorporation of planned formative feedback from decentralization in the Lira district (Figure 2).

In this study, a package of implementation strategies (Table 2) will be employed to support a decentralized SAP delivery strategy to HC III/IV. This will be centered around the introduction of the ACT application further elaborated below.

Table 2. ADD-RHD Implementation strategies mapped according to Expert Recommendations for Implementing Change (ERIC) discreet implementation strategies (33)

Strategy	Details
Assess for readiness and identify barriers and facilitators	Assessment for readiness will be done through facility visits, surveys, and engagement of local and district health officers (DHO). Patient and provider interviews will identify barriers and facilitators to decentralization. Key stakeholder and community engagement on decentralization logistics will serve to establish key components of the process.
Change of service sites (decentralization)	Four health facilities were identified based on patient clusters and distances from their residences primarily geared at increasing access and reducing distances travelled.
Training Health Care workers (HCWs)/ develop educational materials	HCW training was planned to include the development of education materials on RHD clinical knowledge, BPG preparation and injection skills, penicillin adverse events recognition and first aid management. A detailed description is provided below.
Change record systems	ACT application was specifically developed as a clinical tool for HCWs through stakeholder engagement and piloting (27). It encompasses in-built tools to enhance patient engagement, including clinicians' monitoring of adherence and quality metrics for monitoring supply stocks. This will replace the current regional registry. A detailed description is provided below.
Purposefully re-examine the implementation	We built in milestones to re-examine implementation activities, identify challenges, and provide feedback and support to health facilities in order to continuously improve the quality of care. This includes looking at the use of ACT for patient management, identifying challenges and giving feedback to healthcare workers in health centres
Identify and prepare champions	Initial assessment for readiness informed the need for local champions at each health centre, selected to drive the implementation by providing support and driving quality improvement activities such as updating stock and supplies data for quality metrics on the ACT application.
Physical supply of medicines*	Although historically used to treat other conditions, such as syphilis, its consistent availability is variable in public facilities in Uganda. Hence, through stakeholder and local engagement, temporary BPG supply was found to be an essential initial component to the success of the intervention at a few facilities. This marked an iterative adaptation in light of short-term regulatory constraints. For some facilities,

	increasing BPG supply through the government system was motivated by history of use, and hence a gap in supply was inevitable during the initial post-decentralization period. Covering this gap was an important aspect to implementation.

*Not a specific ERIC implementation strategy. DHO, District Health Officer; HCW, Health Care Worker; RHD, Rheumatic Heart Disease; ACT, Active Community Case Management Tool; BPG, Benzathine Penicillin G

ACT application

The ACT application is a digital tool-kit designed to build on REDCap, the current research database. The application incorporates several important features for RHD control including; 1) Availability of a simplified, interactive record of patients' administered BPG injections with automatic adherence calculations and relevant patient details, investigations and management; 2) A 'manage my patient' feature that allows clinicians to track patient status by due or missed visits that integrates with a clinician-facing reminder function, and 3) Monitoring of medicinal and supply stocks at facility and central levels. ACT is a small-scale medical record application built with the overarching goal of its integration for RHD care nationally and internationally, with potential to be replicated for use in other chronic disease management. Table 1 summarizes the current and new approach with regards to ACT as a novel electronic tool. The use of technology enhanced tools in this setting will require some additional efforts. This was informed by the pilot training where many HCWs were not conversant with digital tools and apps. The feedback was then used to develop a simplified application version for HCWs (27). Secondly, an offline feature was added to ACT to ensure interruptions are minimized given the instability with internet connectivity in this setting. Further, initial on-going site support visits have been planned at pre-determined intervals (frequently at first and then more spaced out) and will serve to provide refresher training on RHD and ACT. Data will be collected around these and incorporated into the implementation evaluation.

Provider education

Training of health workers from health centres will be central to this project. Whilst advocacy and awareness of RHD has been increasing due to established research efforts, a large gap remains in provider RHD competency. Recent research found that less than 25% of facilities across several Ugandan districts had received any RHD training in the past two years and only 11% and 8% HC III and IVs had any RHD guidelines (34). Further, limited RHD knowledge was a prominent theme in published health care provider interviews, who expressed a strong desire for training (34).

Currently, service provision of BPG for RHD in HC III/IV is not systematically undertaken. This informed an initial pilot training of representatives from each of the selected HCIII/IV facilities for decentralization in Lira. The pilot identified deficiencies in specific areas that were instrumental in tailoring educational materials developed for pre-decentralization training. We found variable but low RHD knowledge and experience among the HCWs. BPG is known to be a difficult injection to administer due to its nature to crystallize and presents challenges for unexperienced workers. A substantial portion of the planned training (and refresher sessions planned periodically thereafter), will focus on the practical aspects of BPG administration, as well as recognition and triage of potential BPG allergic reactions and anaphylaxis. The second set of training materials will consist of introduction to the ACT application. Additionally, a standard operating procedure (SOP) was developed, which will serve as the guideline for all decentralization procedures in health facilities in both districts.

'Champions', will be identified by the RHD research nurses based at the regional hospitals. The relationship between them and the staff at the health centres has been fostered overtime, giving them an advantage to identify overall motivated staff in different aspects of decentralization- with a particular emphasis on electronic record patient management and follow-up. Champions will be identified for each health centre in the first few months after decentralization and geared to drive the implementation and continuous support Inclusion of medical records personnel was not initially planned for. However, the pilot training revealed that these personnel are more technologically competent and including them would facilitate support at the health centres throughout the implementation".

Study population and recruitment

All eligible RHD registrants will be approached by trained study staff. After an explanation of the study is provided, the registrants will be invited to participate in decentralization. Registrants will be presented with the option to receive their care at one of the four community HCs selected in each district that is closest to them. Participation for all participants is voluntary and informed consent or assent from a parent or guardian (for those > 8 but < 18 years) will be sought and signed before enrolment.

Participant eligibility

Inclusion criteria. Eligible participants for decentralization will be all RHD registrants who live within 20 km of a participating health centres.

Exclusion criteria. Registrants will be ineligible for participation if they have severe RHD - shown to be associated with an increased risk of a vasovagal mediated sudden deterioration during or immediately after a BPG injection; caution has been issued on BPG use in this population (35). According to these recommendations, we will exclude patients with severe mitral stenosis, severe aortic regurgitation or stenosis, ventricular dysfunction (EF < 50%) or with advanced symptoms (NYHA class III/IV) (35) as ascertained by echocardiography performed within 6 months prior to decentralization.

Registrants consenting to decentralization will have the necessary information regarding their care at participating health centres given to them during their last visit at the regional hospital. Following this, registration of health centre nurses to the ACT application will commence. Given the novelty of systematic RHD care delivery in clinics, the research team will be on-site (at the health centres) for the first week and frequently thereafter, according to a documented schedule in order to provide the necessary support during this period. This will be phased out slowly over three to six months. As one of the key implementation strategies, we purposefully planned to re-examine implementation activities- including patient flow at clinics and the use of ACT for patient management. Any challenges identified will be attended to through a feedback process between healthcare workers in health centres, the research team and study administrators.

Implementation outcomes

For the primary implementation outcome, BPG adherence will be measured as a proxy for post-implementation healthcare utilization among registrants. The annualized proportion of persons who have ≥ 80% of days covered pre- and post-decentralization will be compared. At the individual level, adherence is calculated as the proportion of days covered over days prescribed BPG (Table 3). Data will be obtained from the ACT application and RHD REDCap registry for baseline pre-decentralization

adherence data. Based on our hypothesis, we will be testing for non-inferiority of SAP adherence, post-implementation.

Table 3. Key metrics collected during baseline data collection

Primary Metric	Operational Definition	Collection Method
BPG Adherence	The proportion of persons who have 80% of days covered. Each registrants' days of coverage will be calculated as: Days of coverage (%) = Days with adequate BPG coverage*/Days prescribed BPG. *Adequate BPG coverage defined as the prescribed interval between BPG injection (i.e. 28, 21, or 14 days).	National Registry and ACT application, based on dates of injections as compared to prescription
Secondary Metrics	**Operational Definition**	**Collection Method**
Retention	Defined as being seen at least twice in a 12-month period for clinical review (outside or in conjunction with BPG delivery)	National Registry and ACT application
Composite Adverse CV events	Combination of new or worsening heart failure, atrial fibrillation, infective endocarditis, and/or recurrent ARF	National Registry and ACT application, supplemented as needed by patient interview
RHD Mortality	Death of an RHD registrant that is determined to be the direct or indirect result of RHD.	Multimodality, direct report from family or hospital/clinic if death was witnessed by medical staff
BPG Stockouts	Number of days with no BPG or BPG-related supplies (needles, syringes, dilutant, lidocaine, etc.) to be tracked individually, and # of days at <20% supply (based on anticipated number of RHD registrants assigned to that clinical location)	ONLY tracked during decentralized care, through both stock inventory by our research staff (monthly surveillance) and reports on the ACT application
BPG, Benzathine Penicillin G; ACT, Active Community Case Management Tool; CV, cardiovascular; RHD, Rheumatic Heart Disease		

The taxonomy of implementation constructs proposed by Proctor et al., (36) will be used to guide the data collection, levels of analysis, and measurement of implementation outcomes, with particular emphasis on acceptability, adoption, penetration, and implementation cost.

Pre-implementation, formative research was planned and undertaken among stakeholders in the two districts to inform the design and logistical aspects of the project. At the start of the study, facility surveys will collect monthly data on clinic staff numbers and roles, availability of drugs (which will inform drug-stock outs) and consumables - with particular emphasis on RHD care-relevant supplies. We will evaluate the implementation outcomes of acceptability, adoption and penetration by conducting a concurrent mixed methods evaluation of the ADD-RHD program (Table 4). Pre/post decentralization patient and provider qualitative interviews using semi-structured questionnaires have been planned within a month prior to decentralization to get in-depths perspectives from potential participants, including foreseen barriers to program roll-out. This was intended to be

formative, and no formal framework will be used. However, six key areas of interest pertaining to decentralization were used to develop *a priori* data extraction template. A matrix-based rapid qualitative analysis will be done and themes and sub-themes generated will enable the incorporation of findings in real-time to optimize the decentralization of RHD care. This was planned as part of implementation iteration (together with a staggered roll-out in Lira and then Gulu district), for quality improvement. Further, database queries, anecdotes, user inquiries and field diaries from support staff will be kept to inform determinants of implementation. In particular, we will collect data on patient use of health centres and return rates (if any) to the regional hospital that will inform acceptability (Table 4). A sub-study will evaluate costs, as an important implementation outcome. High out of pocket costs have been previously documented to be associated with the current centralized care (3). It is postulated that a decentralized model will result in reduction of out of pocket expenditures. To enable this evaluation, pre-planned patient surveys, time and motion studies (37) and facility cost data will be used in an embedded economic evaluation and reported separately from the main study. Furthermore, time and motion studies will be incorporated to evaluate any disruptions to care and potential distribution of valuable manpower resources which will be valuable for planning and scaling the intervention if it were successful.

Table 4. Data sources for the evaluation of implementation outcomes

	Definition (Proctor et al, 2011) (36)	**Provider Level**	**Patient Level**	**Facility Level**	**ACT Application Audits**	**Record Audit at RRH Visits**
Acceptability	Relates to perceptions on suitability and agreeability of the innovation and the satisfaction among stakeholders. Analysis will be at the patient and provider level.	Provider pre-/post-decentralization interviews	Patient pre-/post-decentralization interviews Coded under acceptability and Health setting preferences	Administrator interview	ACT usage audit/data queries Documented ACT application changes	RRH injection record audits; Self-decentralization rates and rates of return to RRH post-decentralization
Adoption	Defined as the intention to take up an innovation; also quoted as "uptake" (Proctor et al, 2011, p.69)(36). In this study adoption will be analyzed at the provider level at the health facilities.	Provider pre-/post-decentralization interviews. Observation Time & Motion study	N/A	Monthly Health facility survey - organization & appropriateness of RHD medicinal and supplies order based on need. Direct observation	ACT usage audit; -Trends of use by HC nurses -Completeness of BPG injections -Use of additional features (Reminder & Update of stock alerts)	Examination of entered data on BPG card versus ACT application
Penetration	Refers to the absorption or incorporation of the practice into the service setting and looks at the integration of the innovation in question. The level of	Provider pre-/post-decentralization interviews. Attendance to RHD cases. Numbers of providers trained versus numbers delivering service	N/A	Monthly Health facility survey - Improvements in medicinal (BPG) and supply shortages Direct observation Regular attendance of RHD patients	Query-generation rates on ACT application Use of paper records for RHD care ACT usage by HC nurses – completion of information and other usage parameters overtime	Reduction in BPG visits to RRH services for decentralized registrants

	analysis is at the health facility level				Rates of re-education for HC nurses on deficient areas identified	
RRH, Regional referral hospital; ACT, Active community case management tool; HC, Health Centre						

Secondary clinical outcomes

Information on secondary clinical outcomes will be reported (Table 3). We will assess the non-inferiority of the decentralized registry on rates of retention at two years post implementation (Table 3). Further, a composite of adverse cardiovascular events, including a combination of new or worsening heart failure, recurrent ARF, atrial fibrillation, infective endocarditis and mortality will be documented during decentralization and records extracted for baseline period rates. In an exploratory analysis, using continuous measures of adherence, we will compare event rates among more- and less-adherent participants to validate the purported dose-response relationship between SAP and ARF, clinical progression of RHD in this context.

Statistical considerations

The primary outcome of the study is to determine whether adherence after decentralization is non-inferior to the baseline adherence recorded for national RHD registry. We propose a one-sided exact binomial test at alpha = 0.025 of the null hypothesis that the proportion of adherent patients during the intervention period is less than baseline by more than 10%. Based on previous experience with this patient population, we expect approximately 150 - 200 persons with RHD will contribute data on adherence during the baseline and intervention periods in Lira and Gulu. We also approximate 75% of these patients will receive 80% of BPG injections. Table 4 provides the expected power (1 – beta) for plausible values of the sample size (n), baseline percent adherent (BPA), and non-inferiority margin. Based on these assumptions, for alpha = 0.025 (one-sided) taking a total of between 150 - 200 participants will provide between 72 - 86% power to reject the null hypothesis of inferiority when the baseline percent adherent is 75% and the NIM is -10%. Thus, we expect to be at least moderately powered to reject the null hypothesis of inferiority at the proposed non-inferiority margin**.**

Patient and Public Involvement

Within the current set-up of RHD care in Uganda, patients attending the main hospital in both districts expressed the problems they faced with long distances travelled from residences (often in rural areas) to come for monthly RHD care at the main hospital. These patients' experiences were incorporated into the design and informed the implementation strategies of this study. Furthermore, stakeholder and community engagement, local and district health administrators were consulted for input on the logistics of the study, including the use of ACT software to enhance decentralized RHD care to the rural and semi-urban health facilities.

Results of the study will be made available to participants and the community through the health facilities and the main hospital in both districts where RHD follow-ups are done.

DISCUSSION

Like many chronic diseases, the successful prevention of RHD entails optimum adherence to monthly BPG injections, the cornerstone of RHD control. Decentralization of health services has long been advocated as a means to improve health service delivery and reach (38). Successful decentralization of care to PHCs resulted in the widespread availability and accessibility of HIV treatments in similar settings, playing a key role in HIV program successes (39). Disease registries have been previously advocated in the early 2000s by organizations such as World Health Federation and RHD Action (40), which outlined minimum standards and guidance for RHD registries. However, these efforts have seen variable country uptake, often characterized by centralized registries, fragile paper records and limitations in quality assurance and continuous monitoring. To date, no modern version of a

decentralized national RHD registry currently exists in LMICs. The ACT application, one of the packages of implementation strategies, was designed to mitigate the static nature of registries and further aid health workers in managing RHD secondary prevention. If successful, this will modernize how we approach RHD secondary prevention in Uganda and other similar settings, where RHD is prevalent. Based on this, and through long-standing partnerships encompassing local, regional and district key stakeholder engagement, we established the feasibility and suitability of ADD-RHD.

ACT is a novel technology-enabled dynamic application that integrates features to empower health workers at all levels of care with supportive tools to track, monitor and better engage RHD patients. In addition, the application will facilitate health centre communication channels to responsible bodies, such as relevant persons in medical supplies and the ministry of health, an important aspect to ensure availability of medicines, supplies and quality improvement. Electronic medical records are yet to be incorporated widely in health facilities in Uganda, hence the tailored simplification for PHCs and initial support provided by the current research collaborative will be valuable and presents a potential for its absorption into future electronic medical records expansion plans (27). Ultimately, the study can be used as a model for chronic disease management by informing how we integrate these digital health systems to enhance patient care in similar settings where HCWs are not necessarily well-versed with computers or technology.

We acknowledge some limitations to this study. Firstly, the study design did not use an external control group, and had a fixed sample size, reflecting the limited cases currently identified and established in the registry from previous screening efforts. The use of fairly robust and more comprehensive mixed-methods with the additional collection of more granular data was designed to mitigate some of these limitations. Another potential limitation is around the ACT application, requiring baseline user comfort with technology and smart phones, which was not the case with some community public health workers. The pilot training informed the development of a simplified application version tailored specifically to the roles of the HCWs (27). In addition, internet connectivity is often unstable is this setting, which informed the incorporation of an offline feature function that may enhance the functionality and uptake of the application. Lastly, several other system-level factors pose potential challenges, including long waiting times, staff shortages and drug availability that are generalizable country-wide, but which may impact implementation. Securing medication by use of external resources in the initial period limits the generalizability without modifications to the health system. However, it demonstrates the values of securing supplies to make improvements and signifies more work needs to be done in this area. Despite evidence regarding SAP, most governments have not developed nor scaled- up RHD programs, limiting access to healthcare available to patients. Ultimately, through the project, there is an opportunity to re-design and equip PHCs to overcome some of these barriers to healthcare and serve as a foundation for scaling up much needed RHD services to different parts of the country.

ETHICS AND DISSEMINATION

This study was approved by the Institutional Review Board at Cincinnati Children's Hospital Medical Center (IRB 2021-0160), and Makerere University School of Medicine Research Ethics Committee (Mak-SOMREC- 2021-61). Participation will be voluntary and informed consent or assent (>8 but <18) will be obtained and signed prior to participation. At completion, study findings will be published in peer-reviewed journals and communicated to the public and key stakeholders.

Word count: 4182

Study Status

The ADD-RHD study was initially approved on 04/03/2021. Decentralization of study participants is currently being finalized in the second site and post-decentralization data collection will follow for 12 months to December 2023. Data analysis is planned to start early 2024, with the full project due for completion in April 2024.

LIST 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
ARF: Acute Rheumatic Fever
BPG: Benzathine Penicillin G
EMR: Electronic Medical Records
HC III/IV: Health Centre III/IV
HCW: health Care Worker
LMIC: Low- and middle Income country
MOH: Ministry of Health
OOP: Out of Pocket
PHC: Primary Health Care
RHD: Rheumatic Heart Disease
SAP: Secondary Antibiotic Prophylaxis

DECLARATIONS

Consent for publication

Not applicable

Data Availability Statement

Data sharing is not applicable as no datasets are generated and/or analysed for this study

Competing interests

The authors declare that they have no competing interests

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Author Contributions

AB, DW, EO, CL, CS, JR and KD initially conceptualized the different aspects of the study. DW, KD, AB, NM, JP, JR, EO, NO, JD, SdL, RS, NF and JA contributed to the study design and proposal. NM, JP, JR, NF, SdL, RS, JA, JK, DN, LM, FO, HN, YS, KD, & DW contributed to the implementation aspects of the study. NM, DW, AB, KD wrote the initial draft of the protocol paper. All authors reviewed, updated and approved the final protocol.

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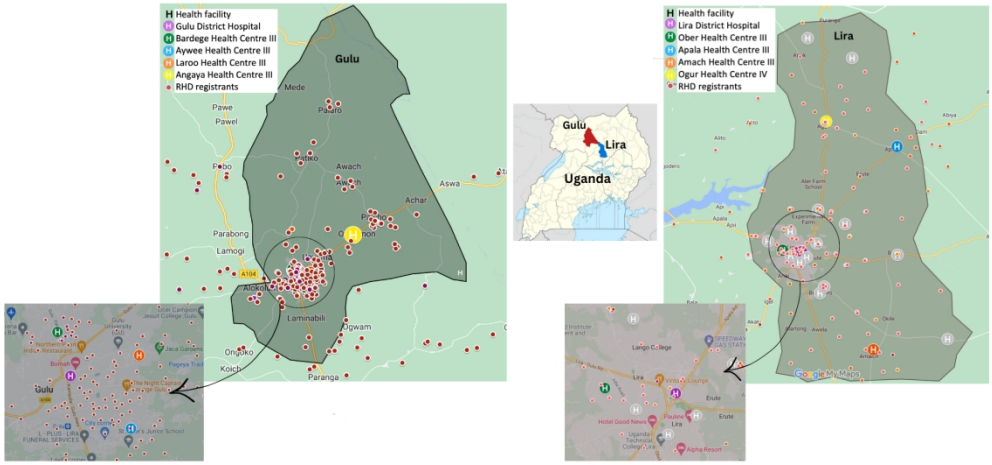

Figure 1. Geographical location of implementation sites in two districts within Uganda. The four selected health centres in Lira and Gulu are chosen according to RHD registrants' geographical density and are designated by H and colour coded.

162x91mm (300 x 300 DPI)

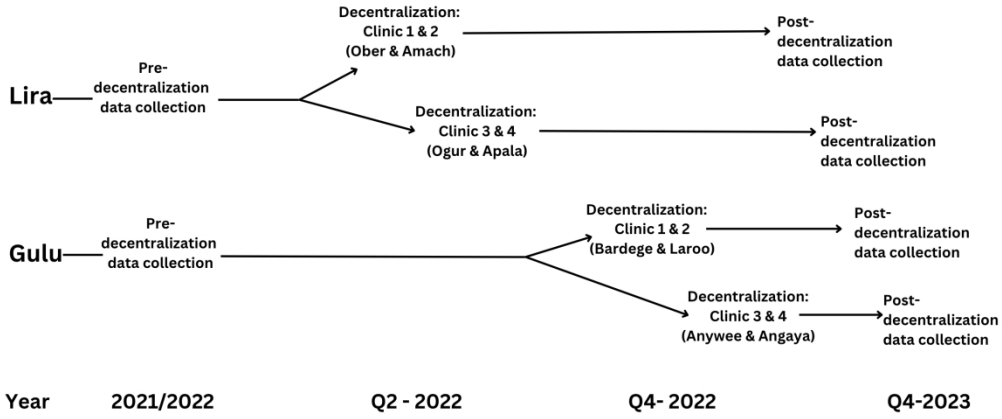

Figure 2. Sequential outline of ADD-RHD implementation plans for health centres in Lira and Gulu districts, Uganda.

201x99mm (300 x 300 DPI)

Standards for Reporting Implementation Studies: the StaRI checklist for completion

The StaRI standard should be referenced as: Pinnock H, Barwick M, Carpenter C, Eldridge S, Grandes G, Griffiths CJ, Rycroft-Malone J, Meissner P, Murray E, Patel A, Sheikh A, Taylor SJC for the StaRI Group. Standards for Reporting Implementation Studies (StaRI) statement. *BMJ* 2017;356:i6795

The detailed Explanation and Elaboration document, which provides the rationale and exemplar text for all these items is: Pinnock H, Barwick M, Carpenter C, Eldridge S, Grandes G, Griffiths C, Rycroft-Malone J, Meissner P, Murray E, Patel A, Sheikh A, Taylor S, for the StaRI group. Standards for Reporting Implementation Studies (StaRI). Explanation and Elaboration document. *BMJ Open* 2017 2017;7:e013318

Notes: A key concept of the StaRI standards is the dual strands of describing, on the one hand, the implementation strategy and, on the other, the clinical, healthcare, or public health intervention that is being implemented. These strands are represented as two columns in the checklist.

The primary focus of implementation science is the implementation strategy (column 1) and the expectation is that this will always be completed.	The evidence about the impact of the intervention on the targeted population should always be considered (column 2) and either health outcomes reported or robust evidence cited to support a known beneficial effect of the intervention on the health of individuals or populations.

The StaRI standardsrefers to the broad range of study designs employed in implementation science. Authors should refer to other reporting standards for advice on reporting specific methodological features. Conversely, whilst all items are worthy of consideration, not all items will be applicable to, or feasible within every study.

Checklist item		Reported on page #	Implementation Strategy	Reported on page #	Intervention
			"Implementation strategy" refers to how the intervention was implemented		"Intervention" refers to the healthcare or public health intervention that is being implemented.
Title and abstract					
Title	**1**	1	Identification as an implementation study, and description of the methodology in the title and/or keywords		
Abstract	**2**	1	Identification as an implementation study, including a description of the implementation strategy to be tested, the evidence-based intervention being implemented, and defining the key implementation and health outcomes.		
Introduction					
Introduction	**3**	2	Description of the problem, challenge or deficiency in healthcare or public health that the intervention being implemented aims to address.		
Rationale	**4**	3	The scientific background and rationale for the implementation strategy (including any underpinning theory/framework/model, how it is expected to achieve its effects and any pilot work).	3, 5	The scientific background and rationale for the intervention being implemented (including evidence about its effectiveness and how it is expected to achieve its effects).

Aims and objectives	**5**	3	The aims of the study, differentiating between implementation objectives and any intervention objectives.		
Methods: description					
Design	**6**	3	The design and key features of the evaluation, (cross referencing to any appropriate methodology reporting standards) and any changes to study protocol, with reasons		
Context	**7**	4, 5	The context in which the intervention was implemented. (Consider social, economic, policy, healthcare, organisational barriers and facilitators that might influence implementation elsewhere).		
Targeted 'sites'	**8**	4, 6	The characteristics of the targeted 'site(s)' (e.g. locations/personnel/resources etc.) for implementation and any eligibility criteria.	8	The population targeted by the intervention and any eligibility criteria.
Description	**9**	6 - 8	A description of the implementation strategy	5	A description of the intervention
Sub-groups	**10**	NA	Any sub-groups recruited for additional research tasks, and/or nested studies are described		
Methods: evaluation					
Outcomes	**11**	9-11	Defined pre-specified primary and other outcome(s) of the implementation strategy, and how they were assessed. Document any pre-determined targets	9-11	Defined pre-specified primary and other outcome(s) of the intervention (if assessed), and how they were assessed. Document any pre-determined targets
Process evaluation	**12**	10	Process evaluation objectives and outcomes related to the mechanism by which the strategy is expected to work		
Economic evaluation	**13**	*	Methods for resource use, costs, economic outcomes and analysis for the implementation strategy	*	Methods for resource use, costs, economic outcomes and analysis for the intervention
Sample size	**14**	11	Rationale for sample sizes (including sample size calculations, budgetary constraints, practical considerations, data saturation, as appropriate)		
Analysis	**15**	11	Methods of analysis (with reasons for that choice)		
Sub-group analyses	**16**	10	Any a priori sub-group analyses (e.g. between different sites in a multicentre study, different clinical or demographic populations), and sub-groups recruited to specific nested research tasks		

Results					
Characteristics	**17**	N/A	Proportion recruited and characteristics of the recipient population for the implementation strategy	N/A	Proportion recruited and characteristics (if appropriate) of the recipient population for the intervention
Outcomes	**18**	N/A	Primary and other outcome(s) of the implementation strategy	N/A	Primary and other outcome(s) of the Intervention (if assessed)
Process outcomes	**19**	N/A	Process data related to the implementation strategy mapped to the mechanism by which the strategy is expected to work		
Economic evaluation	**20**	N/A	Resource use, costs, economic outcomes and analysis for the implementation strategy	N/A	Resource use, costs, economic outcomes and analysis for the intervention
Sub-group analyses	**21**	N/A	Representativeness and outcomes of subgroups including those recruited to specific research tasks		
Fidelity/ adaptation	**22**	N/A	Fidelity to implementation strategy as planned and adaptation to suit context and preferences	N/A	Fidelity to delivering the core components of intervention (where measured)
Contextual changes	**23**	N/A	Contextual changes (if any) which may have affected outcomes		
Harms	**24**	N/A	All important harms or unintended effects in each group		
Discussion					
Structured discussion	**25**	12	Summary of findings, strengths and limitations, comparisons with other studies, conclusions and implications		
Implications	**26**	12	Discussion of policy, practice and/or research implications of the implementation strategy (specifically including scalability)	12	Discussion of policy, practice and/or research implications of the intervention (specifically including sustainability)
General					
Statements	**27**	13 - 14	Include statement(s) on regulatory approvals (including, as appropriate, ethical approval, confidential use of routine data, governance approval), trial/study registration (availability of protocol), funding and conflicts of interest		

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Evaluating the implementation of a dynamic digital application to enable community-based decentralisation of rheumatic heart disease case management in Uganda: protocol for a hybrid type III effectiveness-implementation study

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Evaluating the implementation of a dynamic digital application to enable community-based decentralisation of rheumatic heart disease case management in Uganda: protocol for a hybrid type III effectiveness-implementation study

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ABSTRACT

Introduction: Rheumatic heart disease (RHD) affects over 39 million people worldwide, the majority in low- and middle- income countries. Secondary antibiotic prophylaxis (SAP), given every 3 to 4 weeks can improve outcomes, provided more than 80% of doses are received. Poor adherence is strongly correlated with the distance travelled to receive prophylaxis. Decentralising RHD care has the potential to bridge these gaps and at least maintain or potentially increase RHD prophylaxis uptake. A package of implementation strategies was developed with the aim of reducing barriers to optimum SAP uptake.

Methods and analysis: A hybrid implementation-effectiveness study type III was designed to evaluate the effectiveness of a package of implementation strategies including a digital, cloud-based application to support decentralised RHD care, integrated into the public healthcare system in Uganda. Our overarching hypothesis is that secondary prophylaxis adherence can be maintained or improved via a decentralisation strategy, compared to the centralised delivery strategy, by increasing retention in care. To evaluate this, eligible RHD patients irrespective of their age enrolled at Lira and Gulu hospital registry sites will be consented for decentralised care at their nearest participating health centre. We estimated a sample size of 150-200 registrants. The primary outcome will be adherence to secondary prophylaxis whilst detailed implementation measures will be collected to understand barriers and facilitators to decentralisation, digital application tool adoption, and ultimately its use and scale-up in the public healthcare system.

Ethics and dissemination: This study was approved by the Institutional Review Board (IRB) at Cincinnati Children's Hospital Medical Center (IRB 2021-0160), and Makerere University School of Medicine Research Ethics Committee (Mak-SOMREC- 2021-61). Participation will be voluntary and informed consent or assent (>8 but <18) will be obtained prior to participation. At completion, study findings will be communicated to the public, key stakeholders and submitted for publication.

Keywords: Rheumatic Heart disease, BPG, Decentralisation, Registries, Technology, Implementation science, Primary health centre

Strengths and limitations of this study

- The study methodology outlines an evaluation approach for decentralised care programs for Rheumatic Heart disease, which has not been described before, integrating an electronic RHD registry for primary health care.
- A range of implementation strategies are incorporated within a robust and iterative methodology that address known barriers to care.
- Two different geographical settings are used for the implementation in Uganda, increasing the external validity.
- The study is limited by the pre/post design and lacks an external control group.
- The small number of participating facilities and patients will limit understanding the effectiveness of the intervention.

INTRODUCTION

Rheumatic Heart Disease (RHD) remains the most commonly acquired heart disease in people under 25 years of age (1). The median age at death, 28 years in Sub- Saharan Africa (2), translates into a large toll on the economically-productive age groups, resulting in rippled economic effects for already impoverished families (3). Furthermore, RHD is a disease associated with marked disparities, disproportionally affecting socioeconomically disadvantaged populations including children, women, poverty-stricken and marginalised minority ethnic groups (4–8). It is estimated that there are 39 million people with RHD globally, surpassing the number of people currently living with HIV/AIDS (4,9). Unlike HIV, which has seen sustained efforts towards control, RHD was not a priority on the international health development agenda for many years. Most low- income countries have no RHD programs in place, resulting in a gross underestimation of the prevalent cases and poor RHD knowledge among the healthcare workforce.

The first global resolution on rheumatic fever and RHD was adopted at the 71st World Health Assembly in 2018. Outlined among the broad clauses of this resolution is for countries to invest in community and primary healthcare workers as well as access to medicines for the prevention and control of RHD (10,11). Secondary antibiotic prophylaxis (SAP), in the form of monthly intramuscular Benzathine penicillin G (BPG), has been shown to be effective in preventing recurrent streptococcal infections - 'strep throat', acute rheumatic fever (ARF), and progression of RHD (12–14). These benefits are contingent on achieving an optimum adherence, at least ≥ 80% coverage of prescribed injections over many years of treatment (14,15). However, adherence is often suboptimal, leaving patients vulnerable to recurrent ARF and disease progression, a significant risk factor for death within eight months of diagnosis (16). Several factors have been shown to impact optimal BPG adherence – including drug supply shortages, distances travelled to the health facilities, and associated costs of attending hospitals for monthly injections (17–19).

Previous research in Uganda identified the distance people currently have to travel to receive routine monthly SAP is a major barrier, and a strong predictor of retention (20,21). This is due in part

to the absent district-level RHD programs in Uganda, where primary health care (PHC) nurses do not have practical skills and tools to efficiently manage BPG delivery for RHD patients, despite the fact that this is well within their scope of practice. Moreover, registries have been identified as an important part of RHD control measures (22–24) and set forth as a priority by RHD experts (25). In practice, centralised registries have often taken the form of static data collection (21), and not geared to scale to the community at large. While RHD programs are not yet operational at the district level in Uganda, we have an opportunity to improve access and uptake of BPG prophylaxis for the small fraction (1-2% of estimated total cases nationally) of people who have been identified and are active in the national RHD disease registry (20). Decentralisation of care to primary health facilities has been employed for other diseases, the most widespread in the region being decentralisation of HIV treatment to PHC nurses, allowing for major scale-up and availability of HIV services to those in-need (26).

Demonstrating that a new approach to RHD care is effective and implementable is important for scaling RHD services more broadly. The capacity within the current centralised approach is insufficient to serve the approximately 200 - 400 thousand persons estimated to be living with RHD in Uganda. Thus, there is a need to bring RHD care into the digital age, where technology-enhanced dynamic tools can be employed to improve RHD care delivery. The ADD-RHD (Active Case Detection and Decentralized Dynamic Registry to Improve the Uptake of Rheumatic Heart Disease Secondary Prevention) study was designed to address the above-mentioned challenges, including long distances to regional hospitals and the lack of a dynamic record system. The study is called "ADD-RHD" in part because the study "adds" RHD care to the list of competencies of PHC nurses in the study sites. As a major component of this study, the Active community case management tool (ACT) that was recently developed and piloted will be introduced in this setting, intended to support clinicians with technology-enhanced support tools (27).

Aims and hypothesis

This study aims to evaluate the effectiveness of a package of implementation strategies that includes: assessment of site readiness, decentralisation of service sites, a new mode of electronic record- keeping, health care worker training, iterative feedback during implementation, identification of champions and physical supply of medicines for improving SAP delivery for RHD care. We hypothesise that this package of strategies will be equivalent to or improve the current SAP adherence and related outcomes for enrolees in the decentralised study locations.

METHODS AND ANALYSIS

Study design

This is a mixed methods, hybrid type III effectiveness-implementation study, that will be integrated into rural and semi-urban primary health centres. This design primarily focuses on the effectiveness of a package of implementation strategies whilst collecting secondary data on clinical outcomes (28). Decentralisation of SAP delivery is postulated to at least preserve the level of adherence, whilst building capacity to scale up service delivery. The primary implementation endpoints will look at the post-implementation healthcare utilisation outcomes among enrolled patients, with a particular focus on SAP adherence (defined as proportion of days covered), which is strongly associated with the clinical outcomes of recurrence of ARF and progression of disease (14). The study will determine whether adherence to SAP post-implementation is non-inferior to the current, centralised care. We estimated a total of 150 - 200 persons with RHD Lira and Gulu will be eligible for decentralisation (statistical considerations below). Further, we will evaluate the acceptability, penetration, adoption, and cost of the implementation.

For secondary clinical outcomes, we will explore the relationship between program and adverse cardiovascular events (recurrent ARF, new or worsening heart failure, atrial fibrillation) and mortality compared to the baseline period. Because of the relatively small number of identified people with RHD in Uganda, and the centralised nature of secondary prophylaxis delivery currently at a small number of referral hospitals, we developed a non-randomised experiment using pre/post methods to demonstrate the impact of a package of strategies on implementation outcomes as well as intermediate clinical outcomes.

Study setting

Current RHD care provision – National registry at central and referral regional hospitals

Presently, a national RHD registry, a collection of clinical data for RHD patients enrolled and known to the healthcare system in Uganda is run centrally by research staff at the Uganda Heart Institute (Kamplala). Initially established in 2010, the registry subsequently expanded to include a satellite centre in Kampala (Lebowa) - and regional registry sites within 3 districts across the country (Mbarara, Gulu and Lira). The current RHD registry-based care in Uganda was initiated to capture people presenting with RHD to tertiary care and has served to establish numbers of those affected together with informing patient status. Dedicated research staff provide, coordinate and monitor routine BPG prophylaxis and RHD-related patient care in the country. The RHD registry is hosted electronically on REDCap, and involves both direct data entry and transfer of paper records into REDCap (29,30). However, the majority of records are paper-based and limited to the centres, which has proven to be outdated and ineffective (Table 1).

The new approach – ADD-RHD

Existing RHD registrants based in Lira and Gulu districts will have their monthly SAP visits decentralised from the current research-nurse led regional hospitals to outpatient settings of selected PHCs staffed by ministry of health nurses (Table 1). In this study, decentralisation is defined as the change of service sites for delivery of SAP for RHD registry patients, from current regional hospitals to district level PHC facilities. As part of the ADD-RHD package, the ACT application (see below) will be introduced.

Table 1. Comparison of current and proposed SAP delivery approaches

	Current Approach – National RHD Registry	**Proposed approach – Decentralised RHD Registry at district level health facilities**
Location	Limited to central and regional referral centres	Expansion to Health centres III/IV (Lira and Gulu districts)
Staff	Dedicated research staff regionally	This approach will incorporate existing MOH staff at HCIII/IV at district and regional hospitals, as well as administrators and different stakeholders from Ministerial representatives
Patient records and data	REDCap/paper-based clinical records • Web-based electronic database largely supporting research activities	ACT application • Keeps track of BPG injections • Automatic adherence calculation • Intended for direct entry by HCWs

	• A mix of direct entry and transfer of paper records have been used. • Not scalable; not enabled to support clinical management.	• Managing patient features categorised for 'due' and 'missed' injections • Iterative – patient reminder integration and tracking; clinician/specialist/MOH representative communication features • Quality metrics - Allows easily generated quality reports for examining overall adherence, referrals for procedures and the ability to compare across facilities and regions. Potentially scalable nationwide for RHD and other chronic illnesses.
SAP, Secondary Antibiotic Prophylaxis; RHD, Rheumatic Heart Disease; HC III/IV, Health Centre III/IV; MOH, Ministry of Health; ACT – Active Community Case Management Tool; HCW – Health Care Worker		

The intervention

The evidenced-based practice, secondary antibiotic prophylaxis, has been proven to be effective in reducing the recurrence of strep throat and acute rheumatic fever, the cascade of events that can progress to RHD (14,15,31). In addition to reducing the progression of RHD, there is evidence that SAP can also induce the regression of clinical RHD (32). Unless contraindicated, BPG is the gold standard and most widely used for RHD secondary prevention (14).

Preparation for decentralisation

In preparation for the study, facility visits, engagement of local and district health officers and consideration of the existing registry were done in order to inform important aspects of the implementation strategy.

Existing RHD registrants were mapped by residence, and consequently, four level 3 and 4 health centres (HCIII/IV) were chosen in each district based on diversity of location (city and rural parts of the districts) and RHD registrant geographical density (Figure 1). This was done in coordination with the local government, involving the District Health Administrator. In Uganda, rural and semi-urban areas are served by primary care health facilities with designated levels 1 – 4, where level 1 is the lowest basic dispensary and 4 with more services such as maternity care.

Initial collection of 12 – 18 months of intensive baseline data of existing RHD registry patients will be done at the Lira and Gulu regional hospitals, where RHD patient care is currently based. Where necessary, patients will be contacted by phone for confirmation and completeness of information in order to determine baseline BPG adherence and retention data prior to decentralisation. This data will be collected on a quarterly basis for important primary and secondary metrics defined.

Decentralisation will be a phased process starting with two of the four clinics in Lira district, followed by the remaining two, with an approximate four-week gap in-between. Thereafter, this will be replicated in Gulu after a period of four – six months to allow incorporation of planned formative feedback from decentralisation in the Lira district (Figure 2).

In this study, a package of implementation strategies (Table 2) will be employed to support a decentralised SAP delivery strategy to HC III/IV. This will be centred around the introduction of the ACT application further elaborated below.

Table 2. ADD-RHD Implementation strategies mapped according to Expert Recommendations for Implementing Change (ERIC) discreet implementation strategies (33)

Strategy	Details
Assess for readiness and identify barriers and facilitators	Assessment for readiness will be done through facility visits, surveys, and engagement of local and district health officers (DHO). Patient and provider interviews will identify barriers and facilitators to decentralisation. Key stakeholder and community engagement on decentralisation logistics will serve to establish key components of the process.
Change of service sites (decentralisation)	Four health facilities were identified based on patient clusters and distances from their residences primarily geared at increasing access and reducing distances travelled.
Training Health Care workers (HCWs)/ develop educational materials	HCW training was planned to include the development of education materials on RHD clinical knowledge, BPG preparation and injection skills, penicillin adverse events recognition and first aid management. A detailed description is provided below.
Change record systems	ACT application was specifically developed as a clinical tool for HCWs through stakeholder engagement and piloting (27). It encompasses in-built tools to enhance patient engagement, including clinicians' monitoring of adherence and quality metrics for monitoring supply stocks. This will replace the current regional registry. A detailed description is provided below.
Purposefully re-examine the implementation	We built in milestones to re-examine implementation activities, identify challenges, and provide feedback and support to health facilities in order to continuously improve the quality of care. This includes looking at the use of ACT for patient management, identifying challenges and giving feedback to healthcare workers in health centres.
Identify and prepare champions	Initial assessment for readiness informed the need for local champions at each health centre, selected to drive the implementation by providing support and driving quality improvement activities such as updating stock and supplies data for quality metrics on the ACT application.
Physical supply of medicines*	Although historically used to treat other conditions, such as syphilis, its consistent availability is variable in public facilities in Uganda. Hence, through stakeholder and local engagement, temporary BPG supply was found to be an essential initial component to the success of the intervention at a few facilities. This marked an iterative adaptation in light of short-term regulatory constraints. For some facilities,

	increasing BPG supply through the government system was motivated by history of use, and hence a gap in supply was inevitable during the initial post-decentralisation period. Covering this gap was an important aspect to implementation.
*Not a specific ERIC implementation strategy. DHO, District Health Officer; HCW, Health Care Worker; RHD, Rheumatic Heart Disease; ACT, Active Community Case Management Tool; BPG, Benzathine Penicillin G.	

ACT application

The ACT application is a digital tool-kit designed to build on REDCap, the current research database. The application incorporates several important features for RHD control including; 1) Availability of a simplified, interactive record of patients' administered BPG injections with automatic adherence calculations and relevant patient details, investigations and management; 2) A 'manage my patient' feature that allows clinicians to track patient status by due or missed visits that integrates with a clinician-facing reminder function, and 3) Monitoring of medicinal and supply stocks at facility and central levels. ACT is a small-scale medical record application built with the overarching goal of its integration for RHD care nationally and internationally, with potential to be replicated for use in other chronic disease management. Table 1 summarises the current and new approach with regards to ACT as a novel electronic tool. The use of technology enhanced tools in this setting will require some additional efforts. This was informed by the pilot training where many HCWs were not conversant with digital tools and apps. The feedback was then used to develop a simplified application version for HCWs (27). Secondly, an offline feature was added to ACT to ensure interruptions are minimised given the instability with internet connectivity in this setting. Further, initial on-going site support visits have been planned at pre-determined intervals (frequently at first and then more spaced out) and will serve to provide refresher training on RHD and ACT. Data will be collected around these and incorporated into the implementation evaluation.

Provider education

Training of health workers from health centres will be central to this project. Whilst advocacy and awareness of RHD has been increasing due to established research efforts, a large gap remains in provider RHD competency. Recent research found that less than 25% of facilities across several Ugandan districts had received any RHD training in the past two years and only 11% and 8% HC III and IVs had any RHD guidelines (34). Further, limited RHD knowledge was a prominent theme in published health care provider interviews, who expressed a strong desire for training (34).

Currently, service provision of BPG for RHD in HC III/IV is not systematically undertaken. This informed an initial pilot training of representatives from each of the selected HCIII/IV facilities for decentralisation in Lira. The pilot identified deficiencies in specific areas that were instrumental in tailoring educational materials developed for pre-decentralisation training. We found variable but low RHD knowledge and experience among the HCWs. BPG is known to be a difficult injection to administer due to its nature to crystallise and presents challenges for unexperienced workers. A substantial portion of the planned training (and refresher sessions planned periodically thereafter), will focus on the practical aspects of BPG administration, as well as recognition and triage of potential BPG allergic reactions and anaphylaxis. The second set of training materials will consist of introduction to the ACT application. Additionally, a standard operating procedure (SOP) was developed, which will serve as the guideline for all decentralisation procedures in health facilities in both districts.

'Champions', will be identified by the RHD research nurses based at the regional hospitals. The relationship between them and the staff at the health centres has been fostered overtime, giving them an advantage to identify overall motivated staff in different aspects of decentralisation, with a particular emphasis on electronic record patient management and follow-up. Champions will be identified for each health centre in the first few months after decentralisation and geared to drive the implementation and continuous support Inclusion of medical records personnel was not initially planned for. However, the pilot training revealed that these personnel are more technologically competent and including them would facilitate support at the health centres throughout the implementation".

Study population and recruitment

All eligible RHD registrants will be approached by trained study staff. After an explanation of the study is provided, the registrants will be invited to participate in decentralisation. Registrants will be presented with the option to receive their care at one of the four community HCs selected in each district that is closest to them. Participation for all participants is voluntary and informed consent or assent from a parent or guardian (for those > 8 but < 18 years) will be sought and signed before enrolment.

Participant eligibility

***Inclusion criteria*:** Eligible participants for decentralisation will be all RHD registrants who live within 20 km of a participating health centres.

Exclusion criteria: Registrants will be ineligible for participation if they have severe RHD - shown to be associated with an increased risk of a vasovagal mediated sudden deterioration during or immediately after a BPG injection; caution has been issued on BPG use in this population (35). According to these recommendations, we will exclude patients with severe mitral stenosis, severe aortic regurgitation or stenosis, ventricular dysfunction (EF < 50%) or with advanced symptoms (NYHA class III/IV) (35) as ascertained by echocardiography performed within 6 months prior to decentralisation.

Registrants consenting to decentralisation will have the necessary information regarding their care at participating health centres given to them during their last visit at the regional hospital. Following this, registration of health centre nurses to the ACT application will commence. Given the novelty of systematic RHD care delivery in clinics, the research team will be on-site (at the health centres) for the first week and frequently thereafter, according to a documented schedule in order to provide the necessary support during this period. This will be phased out slowly over three to six months. As one of the key implementation strategies, we purposefully planned to re-examine implementation activities- including patient flow at clinics and the use of ACT for patient management. Any challenges identified will be attended to through a feedback process between healthcare workers in health centres, the research team and study administrators.

Implementation outcomes

For the primary implementation outcome, BPG adherence will be measured as a proxy for post-implementation healthcare utilisation among registrants. The annualised proportion of persons who have ≥ 80% of days covered pre- and post-decentralisation will be compared. At the individual level, adherence is calculated as the proportion of days covered over days prescribed BPG (Table 3). Data will be obtained from the ACT application and RHD REDCap registry for baseline pre-decentralisation

adherence data. Based on our hypothesis, we will be testing for non-inferiority of SAP adherence, post-implementation.

Table 3. Key metrics collected during baseline data collection

Primary Metric	Operational Definition	Collection Method
BPG Adherence	The proportion of persons who have 80% of days covered. Each registrants' days of coverage will be calculated as: Days of coverage (%) = Days with adequate BPG coverage*/Days prescribed BPG. *Adequate BPG coverage defined as the prescribed interval between BPG injection (i.e. 28, 21, or 14 days).	National Registry and ACT application, based on dates of injections as compared to prescription
Secondary Metrics	**Operational Definition**	**Collection Method**
Retention	Defined as being seen at least twice in a 12-month period for clinical review (outside or in conjunction with BPG delivery)	National Registry and ACT application
Composite Adverse CV events	Combination of new or worsening heart failure, atrial fibrillation, infective endocarditis, and/or recurrent ARF	National Registry and ACT application, supplemented as needed by patient interview
RHD Mortality	Death of an RHD registrant that is determined to be the direct or indirect result of RHD	Multimodality, direct report from family or hospital/clinic if death was witnessed by medical staff
BPG Stockouts	Number of days with no BPG or BPG-related supplies (needles, syringes, dilutant, lidocaine, etc.) to be tracked individually, and # of days at <20% supply (based on anticipated number of RHD registrants assigned to that clinical location)	ONLY tracked during decentralised care, through both stock inventory by our research staff (monthly surveillance) and reports on the ACT application
BPG, Benzathine Penicillin G; ACT, Active Community Case Management Tool; CV, cardiovascular; RHD, Rheumatic Heart Disease		

The taxonomy of implementation constructs proposed by Proctor et al., (36) will be used to guide the data collection, levels of analysis, and measurement of implementation outcomes, with particular emphasis on acceptability, adoption, penetration, and implementation cost.

Pre-implementation, formative research was planned and undertaken among stakeholders in the two districts to inform the design and logistical aspects of the project. At the start of the study, facility surveys will collect monthly data on clinic staff numbers and roles, availability of drugs (which will inform drug-stock outs) and consumables - with particular emphasis on RHD care-relevant supplies. We will evaluate the implementation outcomes of acceptability, adoption and penetration by conducting a concurrent mixed methods evaluation of the ADD-RHD program (Table 4). Pre/post decentralisation patient and provider qualitative interviews using semi-structured questionnaires have been planned within a month prior to decentralisation to get in-depths perspectives from potential participants, including foreseen barriers to program roll-out. This was intended to be

formative, and no formal framework will be used. However, six key areas of interest pertaining to decentralisation were used to develop *a priori* data extraction template. A matrix-based rapid qualitative analysis will be done and themes and sub-themes generated will enable the incorporation of findings in real-time to optimise the decentralisation of RHD care. This was planned as part of implementation iteration (together with a staggered roll-out in Lira and then Gulu district), for quality improvement. Further, database queries, anecdotes, user inquiries and field diaries from support staff will be kept to inform determinants of implementation. In particular, we will collect data on patient use of health centres and return rates (if any) to the regional hospital that will inform acceptability (Table 4). A sub-study will evaluate costs, as an important implementation outcome. High out of pocket costs have been previously documented to be associated with the current centralised care (3). It is postulated that a decentralised model will result in reduction of out-of-pocket expenditures. To enable this evaluation, pre-planned patient surveys, time and motion studies (37) and facility cost data will be used in an embedded economic evaluation and reported separately from the main study. Furthermore, time and motion studies will be incorporated to evaluate any disruptions to care and potential distribution of valuable manpower resources which will be valuable for planning and scaling the intervention if it were successful.

Table 4. Data sources for the evaluation of implementation outcomes

	Definition (Proctor et al, 2011) (36)	**Provider Level**	**Patient Level**	**Facility Level**	**ACT Application Audits**	**Record Audit at RRH Visits**
Acceptability	Relates to perceptions on suitability and agreeability of the innovation and the satisfaction among stakeholders. Analysis will be at the patient and provider level.	Provider pre-/post-decentralisation interviews	Patient pre-/post-decentralisation interviews Coded under acceptability and health setting preferences	Administrator interview	ACT usage audit/data queries. Documented ACT application changes.	RRH injection record audits Self-decentralisation rates and rates of return to RRH post-decentralisation
Adoption	Defined as the intention to take up an innovation; also quoted as "uptake" (Proctor et al, 2011, p.69)(36). In this study adoption will be analysed at the provider level at the health facilities.	Provider pre-/post-decentralisation interviews Observation Time & Motion study	N/A	Monthly Health facility survey - organisation & appropriateness of RHD medicinal and supplies order based on need. Direct observation.	ACT usage audit -Trends of use by HC nurses -Completeness of BPG injections -Use of additional features (Reminder & Update of stock alerts)	Examination of entered data on BPG card versus ACT application
Penetration	Refers to the absorption or incorporation of the practice into the service setting and looks at the integration of the innovation in question. The level of	Provider pre-/post-decentralisation interviews. Attendance to RHD cases. Numbers of providers trained versus numbers delivering service.	N/A	Monthly Health facility survey - Improvements in medicinal (BPG) and supply shortages Direct observation Regular attendance of RHD patients	Query-generation rates on ACT application Use of paper records for RHD care ACT usage by HC nurses – completion of information and other usage parameters overtime	Reduction in BPG visits to RRH services for decentralised registrants

	analysis is at the health facility level.				Rates of re-education for HC nurses on deficient areas identified	
RRH, Regional referral hospital; ACT, Active community case management tool; HC, Health Centre.						

Secondary clinical outcomes

Information on secondary clinical outcomes will be reported (Table 3). We will assess the non-inferiority of the decentralised registry on rates of retention at two years post implementation (Table 3). Further, a composite of adverse cardiovascular events, including a combination of new or worsening heart failure, recurrent ARF, atrial fibrillation, infective endocarditis and mortality will be documented during decentralisation and records extracted for baseline period rates. In an exploratory analysis, using continuous measures of adherence, we will compare event rates among more- and less-adherent participants to validate the purported dose-response relationship between SAP and ARF, clinical progression of RHD in this context.

Statistical considerations

The primary outcome of the study is to determine whether adherence after decentralisation is non-inferior to the baseline adherence recorded for national RHD registry. We propose a one-sided exact binomial test at alpha = 0.025 of the null hypothesis that the proportion of adherent patients during the intervention period is less than baseline by more than 10%. Based on previous experience with this patient population, we expect approximately 150 - 200 persons with RHD will contribute data on adherence during the baseline and intervention periods in Lira and Gulu. We also approximate 75% of these patients will receive 80% of BPG injections. Based on these assumptions, a one-sided alpha of 0.025, taking a total of between 150 - 200 participants will provide between 72 - 86% power to reject the null hypothesis of inferiority when the baseline percent adherent is 75% and the NIM is -10%. Thus, we expect to be at least moderately powered to reject the null hypothesis of inferiority at the proposed non-inferiority margin**.**

Patient and public involvement

Within the current set-up of RHD care in Uganda, patients attending the main hospital in both districts expressed the problems they faced with long distances travelled from residences (often in rural areas) to come for monthly RHD care at the main hospital. These patients' experiences were incorporated into the design and informed the implementation strategies of this study. Furthermore, stakeholder and community engagement, local and district health administrators were consulted for input on the logistics of the study, including the use of ACT software to enhance decentralised RHD care to the rural and semi-urban health facilities.

Results of the study will be made available to participants and the community through the health facilities and the main hospital in both districts where RHD follow-ups are done.

ETHICS AND DISSEMINATION

This study was approved by the Institutional Review Board at Cincinnati Children's Hospital Medical Center (IRB 2021-0160), and Makerere University School of Medicine Research Ethics Committee (Mak-SOMREC- 2021-61). Participation will be voluntary and informed consent or assent (>8 but <18) will be obtained and signed prior to participation.

At completion, study findings will be published in peer-reviewed journals and communicated to the public and key stakeholders.

The ADD-RHD study was initially approved on 04/03/2021. Decentralisation of study participants is currently being finalised in the second site and post-decentralisation data collection will follow for

12 months to December 2023. Data analysis is planned to start early 2024, with the full project due for completion in April 2024.

DISCUSSION

Like many chronic diseases, the successful prevention of RHD entails optimum adherence to monthly BPG injections, the cornerstone of RHD control. Decentralisation of health services has long been advocated as a means to improve health service delivery and reach (38). Successful decentralisation of care to PHCs resulted in the widespread availability and accessibility of HIV treatments in similar settings, playing a key role in HIV program successes (39). Disease registries have been previously advocated in the early 2000s by organisations such as World Health Federation and RHD Action (40), which outlined minimum standards and guidance for RHD registries. However, these efforts have seen variable country uptake, often characterised by centralised registries, fragile paper records and limitations in quality assurance and continuous monitoring. To date, no modern version of a decentralised national RHD registry currently exists in LMICs. The ACT application, one of the packages of implementation strategies, was designed to mitigate the static nature of registries and further aid health workers in managing RHD secondary prevention. If successful, this will modernise how we approach RHD secondary prevention in Uganda and other similar settings, where RHD is prevalent. Based on this, and through long-standing partnerships encompassing local, regional and district key stakeholder engagement, we established the feasibility and suitability of ADD-RHD.

ACT is a novel technology-enabled dynamic application that integrates features to empower health workers at all levels of care with supportive tools to track, monitor and better engage RHD patients. In addition, the application will facilitate health centre communication channels to responsible bodies, such as relevant persons in medical supplies and the ministry of health, an important aspect to ensure availability of medicines, supplies and quality improvement. Electronic medical records are yet to be incorporated widely in health facilities in Uganda, hence the tailored simplification for PHCs and initial support provided by the current research collaborative will be valuable and presents a potential for its absorption into future electronic medical records expansion plans (27). Ultimately, the study can be used as a model for chronic disease management by informing how we integrate these digital health systems to enhance patient care in similar settings where HCWs are not necessarily well-versed with computers or technology.

We acknowledge some limitations to this study. Firstly, the study design did not use an external control group, and had a fixed sample size, reflecting the limited cases currently identified and established in the registry from previous screening efforts. The use of fairly robust and more comprehensive mixed-methods with the additional collection of more granular data was designed to mitigate some of these limitations. Another potential limitation is around the ACT application, requiring baseline user comfort with technology and smart phones, which was not the case with some community public health workers. The pilot training informed the development of a simplified application version tailored specifically to the roles of the HCWs (27). In addition, internet connectivity is often unstable is this setting, which informed the incorporation of an offline feature function that may enhance the functionality and uptake of the application. Lastly, several other system-level factors pose potential challenges, including long waiting times, staff shortages and drug availability that are generalisable country-wide, but which may impact implementation. Securing medication by use of external resources in the initial period limits the generalisability without modifications to the health system. However, it demonstrates the values of securing supplies to make improvements and signifies more work needs to be done in this area. Despite evidence regarding SAP, most governments have not developed nor scaled- up RHD programs, limiting access to healthcare available to patients. Ultimately, through the project, there is an opportunity to re-

design and equip PHCs to overcome some of these barriers to healthcare and serve as a foundation for scaling up much needed RHD services to different parts of the country.

LIST 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
ARF: Acute Rheumatic Fever
BPG: Benzathine Penicillin G
EMR: Electronic Medical Records
HC III/IV: Health Centre III/IV
HCW: health Care Worker
LMIC: Low- and middle Income country
MOH: Ministry of Health
OOP: Out of Pocket
PHC: Primary Health Care
RHD: Rheumatic Heart Disease
SAP: Secondary Antibiotic Prophylaxis

DECLARATIONS

Consent for publication

Not applicable.

Data availability statement

Data sharing is not applicable as no datasets are generated and/or analysed for this study

Competing interests

The authors declare that they have no competing interests

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Contributors

AB, DW, EO, CL, CS, JR and KD initially conceptualised the different aspects of the study. DW, KD, AB, NM, JP, JR, EO, NO, JD, SdL, RS, NF and JA contributed to the study design and proposal. NM, JP, JR, NF, SdL, RS, JA, JK, DN, LM, FO, HN, YS, KD, & DW contributed to the implementation aspects of the study. NM, DW, AB, KD wrote the initial draft of the protocol paper. All authors reviewed, updated and approved the final protocol.

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FIGURE TITLES/LEGENDS

Figure 1. Geographical location of implementation sites in two districts within Uganda
The four selected health centres (H) in Lira and Gulu (color coded above), were chosen according to RHD registrants' geographical density.

Figure 2. Sequential outline of ADD-RHD implementation plans for health centres in Lira and Gulu districts, Uganda

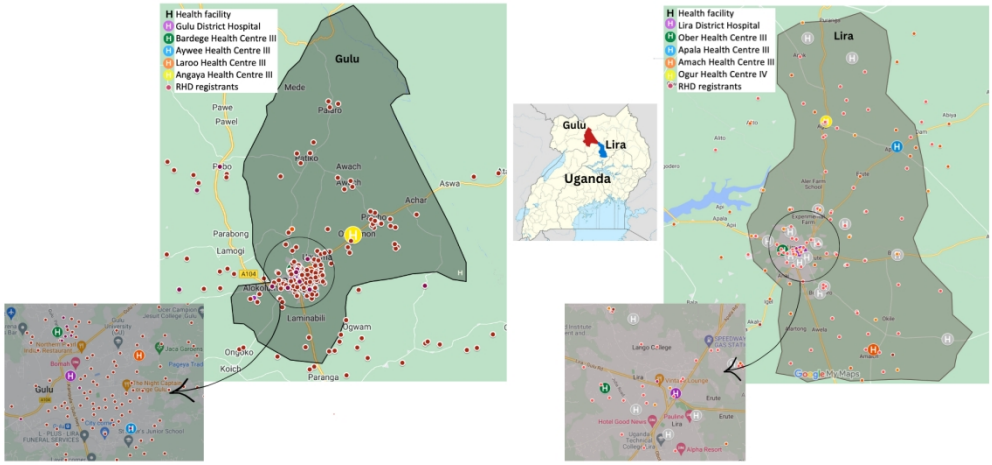

Figure 1. Geographical location of implementation sites in two districts within Uganda. The four selected health centres in Lira and Gulu are chosen according to RHD registrants' geographical density and are designated by H and colour coded.

162x91mm (300 x 300 DPI)

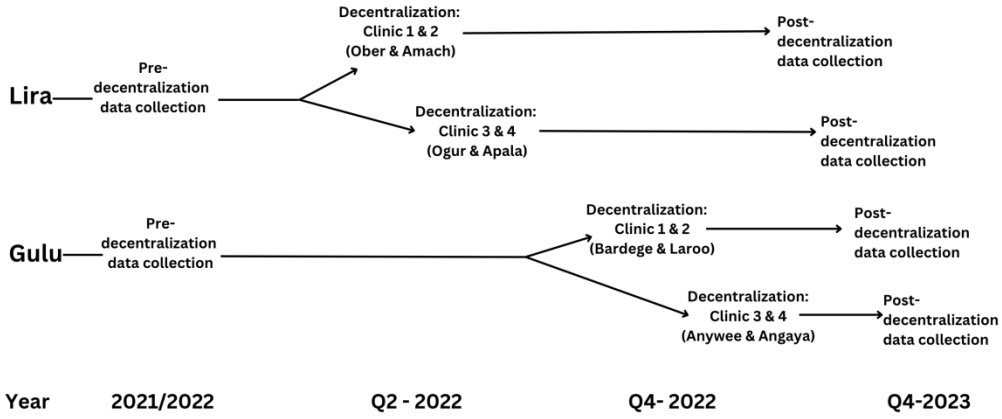

Figure 2. Sequential outline of ADD-RHD implementation plans for health centres in Lira and Gulu districts, Uganda.

201x99mm (300 x 300 DPI)

Standards for Reporting Implementation Studies: the StaRI checklist for completion

The StaRI standard should be referenced as: Pinnock H, Barwick M, Carpenter C, Eldridge S, Grandes G, Griffiths CJ, Rycroft-Malone J, Meissner P, Murray E, Patel A, Sheikh A, Taylor SJC for the StaRI Group. Standards for Reporting Implementation Studies (StaRI) statement. *BMJ* 2017;356:i6795

The detailed Explanation and Elaboration document, which provides the rationale and exemplar text for all these items is: Pinnock H, Barwick M, Carpenter C, Eldridge S, Grandes G, Griffiths C, Rycroft-Malone J, Meissner P, Murray E, Patel A, Sheikh A, Taylor S, for the StaRI group. Standards for Reporting Implementation Studies (StaRI). Explanation and Elaboration document. *BMJ Open* 2017 2017;7:e013318

Notes: A key concept of the StaRI standards is the dual strands of describing, on the one hand, the implementation strategy and, on the other, the clinical, healthcare, or public health intervention that is being implemented. These strands are represented as two columns in the checklist.

The primary focus of implementation science is the implementation strategy (column 1) and the expectation is that this will always be completed.	The evidence about the impact of the intervention on the targeted population should always be considered (column 2) and either health outcomes reported or robust evidence cited to support a known beneficial effect of the intervention on the health of individuals or populations.

The StaRI standardsrefers to the broad range of study designs employed in implementation science. Authors should refer to other reporting standards for advice on reporting specific methodological features. Conversely, whilst all items are worthy of consideration, not all items will be applicable to, or feasible within every study.

Checklist item		Reported on page #	Implementation Strategy	Reported on page #	Intervention
			"Implementation strategy" refers to how the intervention was implemented		"Intervention" refers to the healthcare or public health intervention that is being implemented.
Title and abstract					
Title	**1**	1	Identification as an implementation study, and description of the methodology in the title and/or keywords		
Abstract	**2**	1	Identification as an implementation study, including a description of the implementation strategy to be tested, the evidence-based intervention being implemented, and defining the key implementation and health outcomes.		
Introduction					
Introduction	**3**	2	Description of the problem, challenge or deficiency in healthcare or public health that the intervention being implemented aims to address.		
Rationale	**4**	3	The scientific background and rationale for the implementation strategy (including any underpinning theory/framework/model, how it is expected to achieve its effects and any pilot work).	3, 5	The scientific background and rationale for the intervention being implemented (including evidence about its effectiveness and how it is expected to achieve its effects).

Aims and objectives	**5**	3	The aims of the study, differentiating between implementation objectives and any intervention objectives.		
Methods: description					
Design	**6**	3	The design and key features of the evaluation, (cross referencing to any appropriate methodology reporting standards) and any changes to study protocol, with reasons		
Context	**7**	4, 5	The context in which the intervention was implemented. (Consider social, economic, policy, healthcare, organisational barriers and facilitators that might influence implementation elsewhere).		
Targeted 'sites'	**8**	4, 6	The characteristics of the targeted 'site(s)' (e.g. locations/personnel/resources etc.) for implementation and any eligibility criteria.	8	The population targeted by the intervention and any eligibility criteria.
Description	**9**	6 - 8	A description of the implementation strategy	5	A description of the intervention
Sub-groups	**10**	NA	Any sub-groups recruited for additional research tasks, and/or nested studies are described		
Methods: evaluation					
Outcomes	**11**	9-11	Defined pre-specified primary and other outcome(s) of the implementation strategy, and how they were assessed. Document any pre-determined targets	9-11	Defined pre-specified primary and other outcome(s) of the intervention (if assessed), and how they were assessed. Document any pre-determined targets
Process evaluation	**12**	10	Process evaluation objectives and outcomes related to the mechanism by which the strategy is expected to work		
Economic evaluation	**13**	*	Methods for resource use, costs, economic outcomes and analysis for the implementation strategy	*	Methods for resource use, costs, economic outcomes and analysis for the intervention
Sample size	**14**	11	Rationale for sample sizes (including sample size calculations, budgetary constraints, practical considerations, data saturation, as appropriate)		
Analysis	**15**	11	Methods of analysis (with reasons for that choice)		
Sub-group analyses	**16**	10	Any a priori sub-group analyses (e.g. between different sites in a multicentre study, different clinical or demographic populations), and sub-groups recruited to specific nested research tasks		

Results					
Characteristics	**17**	N/A	Proportion recruited and characteristics of the recipient population for the implementation strategy	N/A	Proportion recruited and characteristics (if appropriate) of the recipient population for the intervention
Outcomes	**18**	N/A	Primary and other outcome(s) of the implementation strategy	N/A	Primary and other outcome(s) of the Intervention (if assessed)
Process outcomes	**19**	N/A	Process data related to the implementation strategy mapped to the mechanism by which the strategy is expected to work		
Economic evaluation	**20**	N/A	Resource use, costs, economic outcomes and analysis for the implementation strategy	N/A	Resource use, costs, economic outcomes and analysis for the intervention
Sub-group analyses	**21**	N/A	Representativeness and outcomes of subgroups including those recruited to specific research tasks		
Fidelity/ adaptation	**22**	N/A	Fidelity to implementation strategy as planned and adaptation to suit context and preferences	N/A	Fidelity to delivering the core components of intervention (where measured)
Contextual changes	**23**	N/A	Contextual changes (if any) which may have affected outcomes		
Harms	**24**	N/A	All important harms or unintended effects in each group		
Discussion					
Structured discussion	**25**	12	Summary of findings, strengths and limitations, comparisons with other studies, conclusions and implications		
Implications	**26**	12	Discussion of policy, practice and/or research implications of the implementation strategy (specifically including scalability)	12	Discussion of policy, practice and/or research implications of the intervention (specifically including sustainability)
General					
Statements	**27**	13 - 14	Include statement(s) on regulatory approvals (including, as appropriate, ethical approval, confidential use of routine data, governance approval), trial/study registration (availability of protocol), funding and conflicts of interest		