Determining the impact of Benzathine penicillin G prophylaxis in children with latent rheumatic heart disease (GOAL trial): Study protocol for a randomized controlled trial

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Background Rheumatic heart disease (RHD) remains a high prevalence condition in low- and middle-income countries. Most individuals with RHD present late, missing the opportunity to benefit from secondary antibiotic prophylaxis. Echocardiographic screening can detect latent RHD, but the impact of secondary prophylaxis in screen-detected individuals is not known.

Methods/Design This trial aims to determine if secondary prophylaxis with every-4-week injectable Benzathine penicillin G (BPG) improves outcomes for children diagnosed with latent RHD. This is a randomized controlled trial in consenting children, aged 5 to 17 years in Northern Uganda, confirmed to have borderline RHD or mild definite RHD on echocardiography, according to the 2012 World Heart Federation criteria. Qualifying children will be randomized to every-4-week injectable intramuscular BPG or no medical intervention and followed for a period of 2 years. Ongoing intervention adherence and retention in the trial will be supported through the establishment of peer support groups for participants in the intervention and control arms. A blinded echocardiography adjudication panel consisting of four independent experts will determine the echocardiographic classification at enrollment and trajectory through consensus review.

The primary outcome is the proportion of children in the BPG-arm who demonstrate echocardiographic progression of latent RHD compared to those in the control arm. The secondary outcome is the proportion of children in the BPG-arm who demonstrate echocardiographic regression of latent RHD compared to those in the control arm. A sample size of 916 participants will provide 90% power to detect a 50% relative risk reduction assuming a 15% progression in the control group. The planned study duration is from 2018–2021.

Discussion Policy decisions on the role of echocardiographic screening for RHD have stalled because of the lack of evidence of the benefit of secondary prophylaxis. The results of our study will immediately inform the standard of care for children diagnosed with latent RHD and will shape, over 2–3 years, practical and scalable programs that could substantially decrease the burden of RHD in our lifetime.

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Background

Rheumatic heart disease (RHD) is the most common acquired cardiovascular disease among children and young adults. Worldwide, there are at least 32.9 million current clinical cases - a prevalence rate of 2.5 to 3.2 cases for every 1000 people.[1] Our research shows that when estimates are expanded to include children with latent RHD, the global burden could increase to as high as 50–80 million prevalent cases.[2] RHD is responsible for between 275,000 and 345,000 annual deaths[3] and accounts for the greatest cardiovascular disease-related loss of disability-adjusted life years in those aged 10–14 years.[4] The global distribution of RHD is uneven and

strongly associated with conditions of social deprivation.[5] The highest prevalence of RHD has been reported in Indigenous Australian and sub-Saharan African populations,[6-8] though the disease remains endemic in most low and middle income countries (LMIC).[9]

RHD is typically diagnosed when advanced and carries a poor prognosis. Compared to the high burden of RHD, diagnosis with rheumatic fever (RF) is less common. Of 1471 patients enrolled in the Ugandan acute rheumatic fever(ARF)/RHD Registry between 2012 and 2016, only 12 were classified as ARF.[10] Recently, the Global Rheumatic Heart Disease Registry Study (REMEDY) in LMICs showed the majority of RHD patients have advanced RHD (63.9%) and complications at time of diagnosis.[11] A single-site study in Uganda found that 85% of patients newly diagnosed with RHD had advanced valvular involvement.[12,13] This is concerning, as many RHD-endemic settings have severely limited capacity to care for patients with advanced RHD. Expectedly, outcomes for patients with RHD are poor with high RHD mortality (3 to 12.5% of patients with RHD die per year) and a low mean age of RHD death (25 years).[19,20]

However, RHD is most commonly a cumulative process and opportunities exist for early intervention. RHD starts with a group A streptococcal (GAS) infection. Untreated, some GAS infections lead to ARF, a systemic inflammatory condition involving the joints, skin, brain, and heart.[14] Around two-thirds of patients with clinical ARF develop RHD.[15] Although the initial attack of ARF can lead to severe valvular disease, RHD is most often insidious in nature, with each recurrent ARF episode causing further valvular damage.[6,14,16] The initial episode(s) of ARF/RHD almost exclusively occur in childhood, but RHD does often not present until early adulthood. The latent period between first episode of ARF and clinically apparent RHD presents an opportunity for early intervention.

Echocardiographic screening has emerged as a powerful tool for early detection of RHD. Echocardiography can visualize RHD before clinical signs appear and is 3 to 10 times more sensitive than clinical examination.[17-19] RHD diagnosed by echocardiography, in the absence of clinical symptoms or history of ARF, has been termed "latent RHD" and can be classified as borderline or definite using criteria published by the World Heart Federation (WHF) in 2012[20] (Table I). In Uganda, screening studies of over 15,000 school children have detected a prevalence of latent RHD of 3.0%.[21,22] These findings have been replicated in other parts of Africa,[23,24] Asia,[25,26] South and Central America[19,27] and the Pacific[28-31] – uncovering a large population with previously undetected RHD that may benefit from early detection and treatment.

The impact of benzathine penicillin G (BPG) prophylaxis on disease progression among children with latent RHD is not known. While not directly comparable, in the pre-BPG era only 20% of children with clinical ARF and RHD showed regression of valvular lesions, while in the post-BPG era, 40–70% improved.[32,33] Additionally, children with recognized ARF are less likely to have recurrence if adherent to BPG prophylaxis.[34] The appropriate management of children with latent RHD is not known and no published recommendations exist.[35-37] While many clinicians prescribe BPG prophylaxis for children with latent RHD, clinical equipoise exists regarding best practice.[36,38] Demonstration of improved outcomes for children with latent RHD given secondary prophylaxis is a critical unknown among international recommendations for a disease amenable to screening.[39]

Longitudinal studies of cohorts of children with latent RHD have not been able to determine the impact of BPG prophylaxis on disease progression. Natural history data (Uganda,[40] India,[41] South Africa,[42] Fiji[43]) among children with latent RHD are limited by the small numbers, limited follow-up times, substantial attrition rates, and varied diagnostic criteria. In addition, children in these studies have inconsistent prescription and adherence to BPG, making it difficult to determine the impact of BPG prophylaxis on disease trajectory. Despite these limitations, these data suggest that approximately two-thirds of children will have persistence or progression of morphological and functional valve abnormalities and up to 25% will progress in the absence of secondary prophylaxis.[42]

The advent of low-cost, highly portable ultrasound technologies, cloud-based image sharing, and remote interpretation makes large-scale echocardiographic screening for latent RHD feasible in several low- and middle-income settings. Identification of latent RHD and

Table I. Operational definitions for RHD

Latent RHD	Rheumatic heart disease that is diagnosed for the first time through active case finding with echocardiographic screening.
Clinical RHD	A symptomatic definition for rheumatic heart disease that has progressed to the point where clinical signs or symptoms are present when diagnosed either clinically or with echocardiographic screening.
Sub-Clinical RHD	A symptomatic definition for rheumatic heart disease that has no clinical signs or symptoms.
Definite RHD	A category of rheumatic heart disease provided by the World Heart Federation Critiera[20] when both morphological and functional alterations in the mitral valve, the aortic valve, or both are seen on echocardiographic screening.
Borderline RHD	A category of rheumatic heart disease provided by the World Heart Federation Critiera[20] when either morphological or functional alterations in the mitral valve or the aortic valve are seen on echocardiographic screening.
Missed clinical RHD	A term used for the *GOAL study* to indicate latent RHD that is moderate or severe in nature at the time of echocardiographic screening. This term captures children who, given proper assessment, could have been detected without echocardiographic screening though routine clinical care.

Table II. Operational definitions for progression and regression of latent RHD

Criteria for Progression	
*Must show evidence of at least one of the following. In all cases, progression will involve a change in diagnostic category (borderline to definite, or definite mild to definite moderate/severe)	
1	New pathological regurgitation at a previously unaffected valve
2	Worsening grade of existing mitral or aortic regurgitation (mild, moderate, severe)[44]
3	Development of two morphological features consistent with RHD (2012 WHF criteria[20]) at a valve that previously had normal morphology, or the addition of one morphological feature at a valve previously only showing a single morphological abnormality
Criteria for regression	
*Must show evidence of at least one of the following. In all cases, regression will involve a change in diagnostic category (mild definite to borderline, or borderline to normal)	
1	Disappearance of existing mitral or aortic regurgitation, or change from pathological regurgitation to physiological regurgitation[20]
2	Decreasing grade of existing mitral or aortic regurgitation (trivial, none)
3	Disappearance of a morphological feature consistent with RHD[20] at a valve that previously had abnormal morphology.

initiation of early BPG prophylaxis is a promising RHD control strategy, but only if prophylaxis changes outcome.[35,37] The utility of screening echocardiography in RHD endemic populations hinges on two critical parameters[1]: the rate of RHD progression and[2] the ability of BPG prophylaxis to improve the disease outcome. Policy decisions on the role of screening for RHD have stalled because of the lack of high-quality data to guide management of latent RHD. The GOAL (GwokO Adunu pa Lutino, meaning Protect the Heart of a Child in Luo) randomized controlled trial is the first study to systematically evaluate efficacy of BPG in patients with latent RHD and aims to provide the critical data needed to determine the standard of care for this population.

Aims and hypothesis

The primary aim of this study is to evaluate the impact of every-4-week prophylactic intramuscular BPG on the progression of latent RHD in children (aged 5–17 years) compared to progression of latent RHD in children who do not receive BPG prophylaxis. The secondary aim of this study is to evaluate the impact of every-4-week prophylactic intramuscular BPG on the regression of latent RHD in children compared to the regression of latent RHD in children who do not receive BPG prophylaxis.

For this study, we will include children with latent RHD who meet WHF criteria[20] for borderline RHD or mild definite RHD (to include no more than mild regurgitation at the mitral or aortic valve, normal mean mitral and aortic valve gradients and normal bi-ventricular function[20]). Children with latent RHD who have more advanced cardiac disease will be excluded. The primary and second outcomes are echocardiographic progression and echocardiographic regression. These outcomes will be determined by a blinded expert adjudication panel who will assess for change between two (baseline and final) randomly displayed echocardiograms though consensus agreement. Change between entry and final echocardiogram could be progression or regression, each of which must meet specific criteria as outlined in Table II.

Methods/design

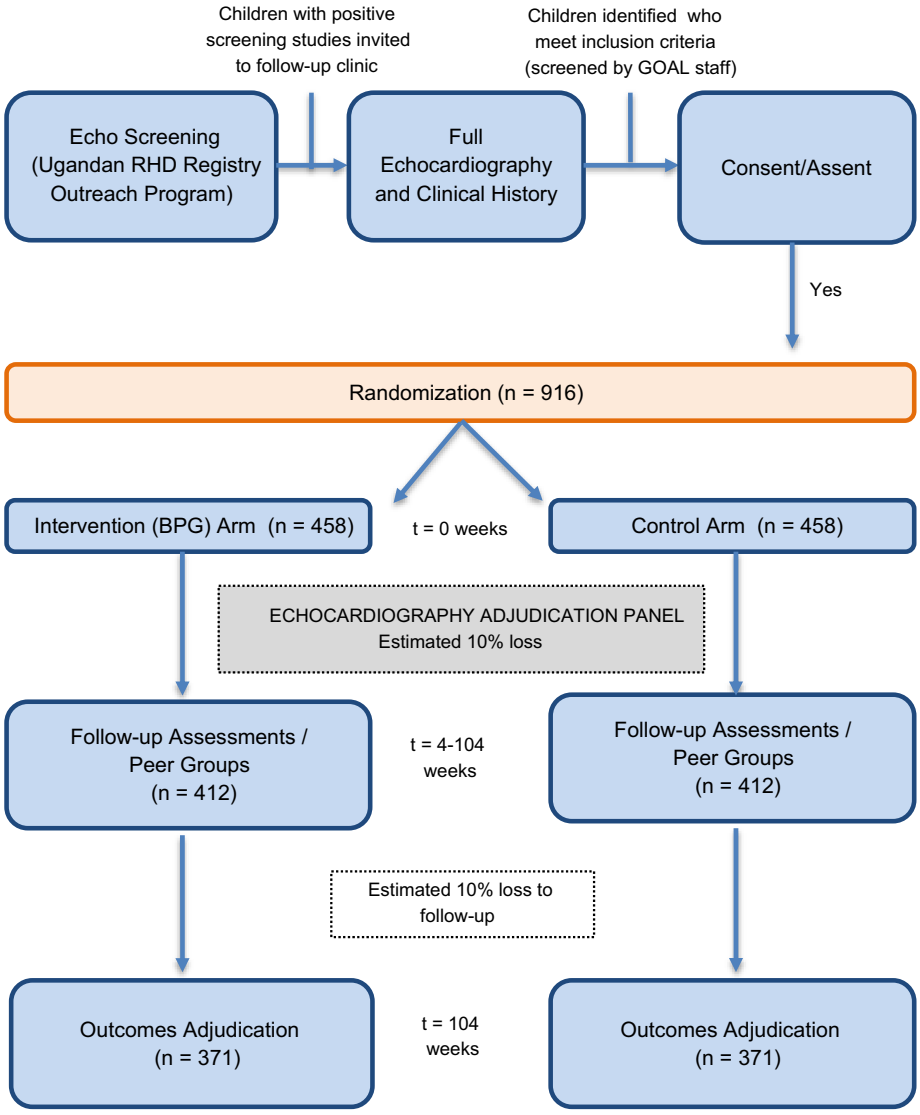
Study design

The GOAL Trial (ClinicalTrials.gov: NCT03346525) is a 2-year, phase III, parallel group, partially blinded (outcomes adjudicators blinded; patients, data collectors, local practitioners not blinded), pragmatic, single-site, randomized controlled trial comparing the outcomes of children (aged 5–17 years) with latent RHD who receive every-4-week intramuscular BPG prophylaxis to those who receive no prophylaxis (Fig. 1). A total of 916 participants will be enrolled in the GOAL trial, with enrollment anticipated to be completed by December 2018 and the study to be completed by December 2020.

Study integrity

This is an investigator-initiated trial supported by the Thrasher Research Fund and multiple private donors/foundations. Other than providing financial support, the sponsors are not involved with the protocol development or the study processes including site selection, management, data collection, and analysis of the results. This trial has been approved by the Human Research Ethics Committee of Makerere University (REF 2018–048), Kampala, Uganda, the Ugandan National Council of Science and Technology (HS2397), and the Ugandan

Fig. 1



Schematic of GOAL protocol.

National Drug Authority (CTA0068) as well as Institutional Review Boards of Children's National Medical Center (#P000010408), Washington DC USA and will be conducted in accordance with the Good Clinical Practice guidelines. The trial was designed in accordance with the CONSORT guidelines. A seven-member trial advisory board, composed of global experts in RHD, worked alongside the investigator team to develop the trial design, endpoints and sample size calculations. Two general community engagement studios and 2 focus groups related specifically to the process of informed consent (40 diverse stakeholders) were conducted in Uganda prior to protocol development and shaped the recruitment, consent/assent, and retention plans.

Study population and recruitment

This outpatient study will be conducted within the infrastructure of the Ugandan National RHD Registry. School-based echocardiographic screening is scheduled for several Northern Ugandan districts in 2018 including Gulu and adjacent Districts. Children who have a positive screening echocardiogram and a confirmatory echocardiogram with a diagnosis of latent RHD at outpatient follow-up—either at Gulu Regional Referral Hospital

cardiology clinic or an off-site cardiology satellite clinic—will be assessed for trial eligibility. When possible, invitation for study participation will occur during the same clinical confirmation visit to ease the burden of repeated visits on children and families. Assessment of eligibility will be performed by a trained researcher to determine if participants meet the inclusion criteria as noted below.

Participant eligibility

Inclusion criteria. Eligible children will be aged between five and 17 years at the time of randomization, have a new diagnosis of latent RHD detected through school-based echocardiographic screening and confirmed during clinical follow-up visit by a physician with expertise in RHD according to the WHF criteria[20] within 30 days of randomization. Eligible children will have a parent/guardian who is able to provide informed consent and when applicable children will provide informed assent.

Exclusion criteria. Children will be ineligible for participation if they have a known history of ARF or RHD, have newly diagnosed RHD by echocardiographic screening considered to be "missed clinical RHD" (Table I) as compared to true latent RHD including: greater than mild pathological valvular regurgitation at the mitral valve or aortic valve; mitral stenosis (mean MV gradient $\geq$4 mmHg)" [20]; aortic stenosis (mean AV gradient $\geq$20mmHg[45]; evidence of structural or functional cardiac defects other than those consistent with RHD that were known prior to or detected through diagnostic echocardiography (except patent foramen ovale, small atrial septal defect, small muscular ventricular septal defect, small patent ductus arteriosus); knowledge of a prior allergic reaction to penicillin; any known conditions predisposing to thrombocytopenia or bleeding, or other contraindications to intramuscular injection; or any known co-morbid conditions (HIV, renal disease, severe malnutrition, among others) that have led to prescription of chronic ($\gg$1 month) antibiotic prophylaxis.

Informed consent and assent

As guided by our community engagement studios, eligible participants and their parent/guardians will undergo a multi-step consent process, which incorporates the contextual cultural importance of consultation with community. First, parents and children will be able to listen to audio recordings of the full consent/assent forms translated into their primary language. Next, children and families will be invited to watch a short educational video created to clarify key trial concepts such as research, randomization, voluntariness. Small group discussions of four to five families will then be moderated by GOAL research nurses. These are designed to foster community and reduce stigma of asking clarifying questions. Following the discussion groups, a research nurse or case manager will obtain individual written consent privately with each family, including asking a series of questions to ensure participants and parents/guardians understand key study elements and providing additional education until understanding is confirmed. Research staff will then provide a paper copy of the informed consent in the language most familiar to the parent/guardian and an assent form in the language most familiar to the minor ($\gg$ = 8 years). Consent and assent will be voluntary and free from coercion. The research staff member conducting the consent discussions will also sign the informed consent and assent form (s). A thumbprint will be accepted as signature for those who prefer.

Randomization, blinding, and echocardiography adjudication

Randomization. Randomization will occur following informed consent utilizing the computer-generated online randomization feature of the REDCap electronic data capture system, housed at Children's National Medical Center.[46] Randomization will be stratified by major WHF category[20] (borderline RHD or definite RHD) and permuted block randomization will be used to ensure balance of allocation. Of the 916 patents enrolled in the study, 458 will be assigned to each of the two study arms: Arm 1 (BPG) or Arm 2 (control) in a 1:1 ratio. The randomization schedule, patient numbering, and sequence of patient number assignments will be prepared and stored within REDCap by an independent statistician. Only the peer group coordinator and a designated case manager will have access to the randomization module and will distribute assignments after consent/assent.

Blinding. For reasons including pragmatic factors, ethical concerns regarding the pain of intramuscular placebo in children and lack of a suitable intramuscular BPG placebo, parents and research staff will not be blinded to the treatment arm. The echocardiography adjudication panel who will determine echocardiographic eligibility and outcomes (see below) will be blinded to treatment arm.

Echocardiography adjudication at enrolment. A blinded expert adjudication panel consisting of four cardiologists with extensive experience in the application of the WHF criteria[20] will meet to definitively assess echocardiograms to determine baseline diagnosis and component criteria of this diagnosis (Fig. 1). Echocardiography adjudication panel decisions will be made by unanimous consensus and will occur blinded to the categorization made at the time of the confirmatory echocardiogram and all clinical and demographic information. Enrolled participants may be reclassified using the WHF criteria or deemed "ineligible" (normal, moderate or severe RHD, or alternate cardiac diagnosis) through this process. The majority of these reclassifications are expected to result in a participant being reclassified from latent RHD to no heart disease, and

Table III. Trial interventions, study measurements, and their frequency

Item/measurement	Brief description/purpose	Frequency
Demographics	Age, gender, type of housing, number of people in household including number aged less than 15 years, school type (day/boarding), WAMI index (Water and sanitation, Assets, Maternal Education, and Income)[49] (measure of household SES)	Pre-enrolment confirmatory visit
Medical/family history	History of RF/RHD, recent sore throat/skin infection, chronic medical conditions, chronic medications, prior hospitalizations/surgeries, complete review of systems, h/o family members (1st degree) with RF/RHD	Pre-enrolment confirmatory visit
Eligibility questionnaire	Inclusion/exclusion criteria	Pre-enrolment confirmatory visit
Informed consent/assent	Per outlined protocol	Enrolment
Randomization	Stratified by WHF criteria (borderline RHD, mild definite RHD)[20]	Enrolment
Concomitant medication/health visit assessment	Review of all interval medications, health center visits, traditional medicine encounters, supported by use of GOAL health passports	Every-4-weeks, phone or in-person with parent/guardian
RF symptom review	RF symptom checklist according to 2015 Jones Criteria[50]	Visit 12, Visit 24, participant interview
Focused echocardiogram	Complete assessment of left-sided cardiac valves and systolic ventricular function utilizing a handheld echocardiography machine	Visit 13
Complete echocardiogram	Complete assessment of left-sided cardiac valves and systolic ventricular function utilizing a full functional echocardiography machine	Visit 26
Participant adverse event review*	Active data collection tool including all common BPG side effects as well as pain, disability, anxiety following last injection.	Every visit, in person with participant prior to next injection
Parental adverse event review	Active data collection tool including all common BPG side effects as well as pain, disability, anxiety following last injection.	Every-4-week phone or in-person with parent/guardian
Adverse event evaluation	GOAL research nurse follow-up, investigation of all reported adverse events	On-going as needed

*Only Arm 1 (BPG). RF, Rheumatic Fever; RHD, Rheumatic Heart Disease; SES, Socioeconomic Status; WAMI Index[49], Water and sanitation, assets, maternal education, and income; WHF, World Heart Federation.

therefore a conservative 10% exclusion rate during adjudication has been built into sample size calculations.

Intervention

Randomization will assign participants to either Arm 1: every-4-week intramuscular BPG for 26 periods (24 months), or Arm 2: no prophylaxis. BPG is packaged as a lyophilised powder in temperature independent single-dose vials of 2.4 million units. BPG will be sourced under the regulation of the Ugandan National Drug Authority from an approved manufacturer. According to best practices[47] the powder will be suspended in 10 ml of sterile water. 5 ml will be withdrawn for children weighing 30 kg or more (1.2 million IU) or 2.5 ml will be withdrawn for children weighing less than 30 kg (600,000 IU). Pain reduction will be achieved with the addition of 0.25 ml of 2% lidocaine/lignocaine, use of the Buzzy® vibrating pain reduction tool,[48] and use of age-appropriate distraction techniques. Most BPG injections will be given by GOAL staff at peer groups and adherence will be tracked through direct observation. In cases where BPG is given remotely, adherence will be tracked through signatures and dates on the participant BPG diary. Adherence will be defined by the continuous variable days of coverage, with each BPG injection covering 28 days. The acceptable window for BPG injection will be between 24–32 days. If an injection is later than the acceptable 32-day window, it will still be given at the earliest possible time, with the subsequent injection rescheduled to meet the minimum acceptable window of 24 days.

Study consultations and peer groups

After randomization, participants in both arms will receive the same number of consultations for the duration of the study (Table III). As guided by our community engagement studios, we will employ a strategy of case managers (one case manager to every 70–80 participants) and peer play/support groups to conduct follow-up and to aid in retention. A participant's case manager will be in routine contact with the parent/guardian by phone to conduct between-visit assessments and to provide reminders about peer group attendance. Home and school visits will be used to reach children and families when connection by phone is not achieved. Support groups will be held on rotating Saturdays for a period of 2 hours and family attendance at support group will be encouraged and supported through transportation refunds. In the case of a missed group, individual arrangements will be made to ensure administration of BPG as soon as possible at the study offices or at the participant's home or school with study staff, or in the case of extended travel, BPG and instructions will be sent with the family and the injection may be given at another health facility (ideally, but not limited to, an established RHD registry site).

Safety monitoring and reporting

DSMB. An independent Data Safety Monitoring Board Committee (DSMB) will be established to oversee the safety and progress the trial. The DSMB will meet via teleconference in the pre-trial period, following

completion of enrollment, and then every 12 months until trial completion.

Adverse events and serious adverse events. The study team will capture unanticipated problems, adverse events (AE), and serious adverse events (SAE) on standard case report forms. Active data collection including Q4 week parent AE review and participant AE review forms will be utilized for those in the BPG-arm to capture quantitative and qualitative AEs known or thought to be associated with intramuscular BPG injection. All AEs will be further investigated by the GOAL research nurse team with follow-up phone calls, house visits, or school visits as appropriate until AE resolution. AEs will be graded by severity and relationship to BPG, and reviewed weekly by the clinical research coordinator, study nurses, and principal investigators. AEs will be reported to the DSMB at biannual meetings and to the Institutional Review Board (IRB) at the yearly continuing review. SAEs will be reported to the DSMB and the IRB within 24–72 hours of occurrence or knowledge of occurrence and will be reported by one of the principal investigators.

Allergy. International data suggests the incidence of allergic reaction to long-term BPG prophylaxis is 3% and the incidence of anaphylactic reaction is 0.2%.[51] Given 371–458 participants (0–20% predicted loss) receiving 26 doses of BPG, we would statistically expect an average of will be 11–14 allergic reactions and 1 anaphylactic event. Anaphylactic events are most likely to occur in the first hour following BPG injection. An emergency anaphylaxis kit will be kept on-site with a plan for rapid triage and transfer to a health facility if anaphylaxis occurs. Minor allergic and hypersensitivity reactions will be tracked through the adverse events checklist. If a reaction, in particular a rash, is considered low-risk for allergy but possibly attributable to BPG, an oral penicillin challenge will be conducted by standard protocol.[52] If the rash or other systemic symptoms reoccur then attribution will be given to penicillin and the child initiated on oral erythromycin (250 mg by mouth twice a day). If an adverse event is considered to be high-risk then alternate antibiotic prophylaxis will be initiated using oral erythromycin without oral challenge. In this situation, children will be given a tracking calendar and be instructed to bring their medication packaging to peer groups. Adherence to oral prophylaxis will be tracked through calendar checks and pill counts.

ARF or advancement to RHD. There are two instances where children in the control arm would be started on BPG prophylaxis prior to the end of the 24-month endpoint. First, participants will be counseled on the signs and symptoms of ARF[50] at the enrolment visit and instructed to contact the research team if these symptoms occur. If ARF is suspected by the research team or clinician, a focused echocardiogram, 12-lead ECG, ESR/CRP, and evidence of recent streptococcal infection (rapid GAS pharyngeal testing, pharyngeal culture, ASO, Anti-DNase B) will be completed at Gulu Regional Referral Hospital. Patients in the control arm who are diagnosed with ARF based on these assessments will be started on BPG prophylaxis, according to well-established standards of care.[50] Similarly, if a child in the BPG arm is proven to have ARF, BPG prophylaxis will be increased to every-3-weeks according to standard escalation protocols.[50] For the purposes of analysis, children with ARF will be kept in their assigned arm with echocardiographic assessment at 2 years (intention to treat analysis). Second, all children will undergo a scheduled mid-study echocardiogram (visit 13, Table II) to monitor for progression to clinical RHD (as defined above, Table I). If a child in the control arm shows progression to clinical RHD, the child will be started on BPG prophylaxis, according to well-established standards of care.[53] For the purposes of analysis, children who progress to clinical RHD will be kept in their assigned arm (intention to treat analysis), and outcome defined as progression, regardless of 24-month echocardiogram results.

Outcome measures. The primary outcome is echocardiographic progression, and the secondary outcome is echocardiographic regression. The 4-member expert blinded expert adjudication panel (as described above) that classified echocardiograms for study enrolment will determine these outcomes. The panel will meet to assess for change between two echocardiograms (baseline echocardiogram at enrolment and final echocardiogram at 2 years) through consensus agreement. Echocardiograms will be displayed in a random side-by-side nature to blind the panel to the acquisition order of the studies. The date of study and all other identifying information will be masked from both the DICOM header and each frame of stills and cine-loops of original and 2-year follow up studies before sharing with the adjudication panel. Progression or regression must meet specific criteria as outlined in Table I.

Statistical analysis plan

Sample size calculation for primary endpoint. Based on the results of published natural history cohorts including data from the Ugandan cohort, we estimated that progression would occur in 7.5 to 12.5% of the in the intervention group and in 15 to 25% of the control group over 24 months. We conservatively assumed the lowest proportions within this range in each of the study arms (i.e. 7.5% vs. 15%) to calculate a sample size of 824 (including 10% attrition). We chose to use power (1-β) of 90%. In addition to the 10% expected loss to follow-up, we added an additional 10% to the sample size to account for loss from enrolment to first adjudication (see above), resulting in a total sample size of 916. While not typical to exclude enrolled patients after randomization, it is necessary because of the pragmatic design of this trial, accommodating the need to capture patients for enrolment as they receive confirmation of latent RHD (during

the first follow-up visit). Given these considerations, our target enrolment is 916 participants, or 458 randomized to each of 2 treatment arms.

Statistical analysis

The modified intention to treat (ITT) population will consist of all randomized participants who are confirmed to have latent RHD by the blinded adjudication panel. The primary and secondary analyses will be done using this modified ITT analysis. All qualifying participants randomized into the study will be analyzed in their study arm, regardless of participant adherence to treatment, crossover to other treatments or withdrawal from the study. The primary aim of the analysis is to compare the proportion of children showing progression of RHD on echocardiogram at 2 years between the two randomized treatment arms. This will be done using a Cochran–Mantel–Haenszel test to compare proportions while accounting for stratification during randomization (borderline RHD or definite RHD). The proportion of children who show progression will be summarized, with 95% confidence intervals, in each treatment arm. The same method will be used to analyze the secondary objective, namely to compare the proportions of children who show regression of RHD on echocardiogram. No interim analyses are planned.

A secondary, exploratory analysis will aim to identify and quantify any identifiable risk factors for progression and/or protective factors for regression among children with latent RHD. These include demographic data (age, gender, type of school, WAMI index of household SES[49]), family history of ARF/RHD, and sub-category of RHD. This analysis will be done through multivariate logistic regression, with presence or absence of progression (and regression) as outcome variables and possible risk factors or protective factors, stratification variables and treatment arm as explanatory variables.

Safety analysis will be done by summarizing all adverse events reported by participants in the intervention arm. For the safety analysis all participants who received any BPG injections will be included, whether subsequently excluded from the modified ITT analysis or not.

Discussion

Echocardiographic screening has emerged as a sensitive and specific tool for the detection of latent RHD[17-19] and has uncovered a large global population of children who may benefit from early intervention.[2] Research to date has focused on the practical aspects of echocardiographic screening including simplified protocols,[54-56] task-sharing with lower level providers,[57-59] use of handheld technology,[22,60] and community impact.[61] However, the question of whether early detection leads to improved disease outcomes has not been answered.[36,38] While historical data support the benefit of BPG secondary prophylaxis as the standard of care for children with clinical RF or RHD, the impact on outcomes for those with latent RHD is not clear. The GOAL trial is the first randomized study of the efficacy of secondary prophylaxis among children with latent RHD.

The GOAL trial has three major strengths that provide the foundation for successful study completion and for broad acceptability and generalizability of results. First, we utilized community-engaged research prior to trial design to inform how the GOAL trial might best be implemented in the Gulu District of Northern Uganda. Community-engaged research is intended to build an authentic partnership to develop research around issues affecting community well-being. Successful community engagement is thought to improve community trust, participant enrollment, and uptake of research findings.[62] The community-engagement studios informed our study design, particularly our approach to recruitment and retention. Through community recommendations we added a discussion group to our consent process to account for community decision making. Also, on recommendation we are organizing our follow-up plan around a case-manager strategy to provide a trusted community member for primary participant contact. Additionally, based on community feedback, follow-up assessments will be structured around peer support/play groups held on Saturdays. These will avoid school and work conflicts, promote the development of a community of peers and families, and provide ongoing parental and participant education and emotional support.[63]

Second, we sought input from a diverse panel of global RHD thought leaders who provided critical feedback on study design, including the operational definition of latent RHD, inclusion and exclusion criteria, outcomes assessment and trial power. This was of particular importance as latent RHD is a relatively new diagnostic category and standardized operational definitions and criteria for progression and regression do not exist (Table I).[36] The GOAL trial is the first randomized clinical trial among patients with latent RHD, and thus may establish these definitions, making broad acceptability among the global RHD community critical. It is our hope that this inclusive approach to study design will lead to rapid uptake, dissemination, and translation of our results into meaningful changes in global practice.

Finally, we will employ a four-member blinded expert echocardiography adjudication panel, which will meet in person to determine study eligibility and outcomes through consensus, according to the WHF criteria.[20] This is of critical importance, as the WHF criteria are not fully objective, and substantial intra-reviewer differences in application can exist,[37] most notably in the early stages of RHD targeted in this trial and within the component criteria.[22,64] We intentionally selected the panel from four distinct RHD research teams (US, Brazil, South Africa, and France/Pacific) to improve rigor and generalizability of the results. Additionally, while participants and research staff will not be blinded to treatment allocation for pragmatic reasons, the adjudication panel will

be blinded to initial classification, demographic data, treatment allocation, and adherence within the BPG arm, and date of study acquisition when determining outcomes.

We also acknowledge some limitations in the study design. Most importantly, while some patients with RHD progress rapidly, there are also indolent presentations with clinical symptoms becoming evident a decade or more after initial RF. Given this natural history, a two-year endpoint may not be long enough to determine the efficacy of secondary prophylaxis. While our expectation is that we have powered our study sufficiently to achieve an answer, the final results at the completion of the trial will be carefully reviewed by the investigators and trial advisory board to determine next steps, with the possibility of trial extension. Echocardiographic trajectory is not a perfect surrogate for clinically important RHD progression and cannot determine the percentage of children who would progress to advanced RHD requiring more aggressive medical and/or interventional therapies. However, utilization of echocardiography for a primary measure of progression will allow for early detection of disease trajectory and enable the GOAL trial to gather meaningful data in a reasonable timeframe in order to inform current practice, where no evidence-based standards currently exist.

Trial status

A total of 916 children were enrolled between July and November 2018, meeting the enrollment target within the planned time frame. Follow-up is expected to continue until December 2020, with final outcomes assessment between August and December 2020.

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