SUMMARY EVALUATION REPORT TEMPLATE

Study Title: Intramuscular vs. Enteral Penicillin Prophylaxis to Prevent Progression of Latent Rheumatic Heart Disease: A non-inferiority randomized trial

NDA CTA Number: CTA 0245

Protocol No. _

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Sponsor: National Institute of Health

REC of record: Uganda Heart Institute REC

REC reference number: HRD 120/251/30

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Study background and Rationale

Rheumatic heart disease (RHD) remains a high prevalence condition in low-and middle-income countries, currently affecting at least 40 million people, many of whom suffer premature death. Most patients with RHD present late, missing the opportunity to benefit from secondary antibiotic prophylaxis. Screening echocardiography in RHD endemic settings identify a large number of children with early, latent RHD, but until recently the effectiveness of prophylaxis to protect children with latent RHD was not known.

In 2018, a randomized controlled trial, (GOAL study) found that children with latent RHD who receive prophylaxis with monthly intramuscular (IM) penicillin prophylaxis are less likely to progress at two-years (0.8% prophylaxis vs. 8.3% no prophylaxis, $p<0.001$). However, despite these results, scale up of echocardiographic screening and early initiation of IM prophylaxis for RHD has a myriad of challenges. Among the most critical

are substantial patient barriers (including pain, missed work/school and high out-of-pocket travel costs) and health system-level barriers (including infrastructure and cost, time, and training) of delivering prolonged courses of IM prophylaxis in low-resource settings. It is of high public health importance to determine if an alternative, less burdensome form of prophylaxis, oral penicillin, is

an effective alternative to IM penicillin in preventing latent RHD progression. Historical

data suggest that IM penicillin has superior efficacy to oral penicillin, but this conclusion warrants contemporary re-examination. The dogma of superiority of IM

penicillin is based on a small set of studies (4 RCTs, ~1000 patients), all from the

United States, in an era that predated echo. Determining if oral penicillin prophylaxis

is not inferior to IM penicillin prophylaxis in preventing latent RHD progression is of

high practical importance, as it will improve the feasibility of an echo screening strategy for advanced RHD prevention in LMICs.

General objective / Study aims

The randomized controlled trial will determine if oral penicillin is non-inferior to IM penicillin prophylaxis in preventing latent RHD progression	

Primary Objectives and Outcome Measures

To compare the proportion of children aged 5-17 years with latent RHD receiving oral penicillin prophylaxis who progress to worse valvular disease at 2-years compared to children who receive IM penicillin prophylaxis.

Secondary Objectives and Outcome Measures

N/A

Study Design

This is a two-arm, partially blinded (adjudicators blinded; patients, data collectors, local practitioners not blinded), pragmatic, randomized, controlled non-inferiority trial among 5-17-year-old children and adolescents with latent RHD comparing disease progression between those who receive twice-daily oral penicillin prophylaxis compared to those who receive monthly IM penicillin prophylaxis for 2 years.

Study Population

Participants aged between 5-17 years with a new diagnosis of latent Rheumatic Heart Disease

Eligibility Criteria

Inclusion Criteria:

1. Is between the ages of 5-17 years and

2. Has a new diagnosis of latent RHD detected through primary or secondary school echocardiographic screening.

3. Has agreed to participate in the study via the study's informed consent/assent process. Questions will be answered and formal consent/assent sought from parent/guardian and child (> 8 years).

Exclusion criteria:

1. Known history of ARF or RHD
2. Newly diagnosed RHD by echo screening considered to be "missed clinical RHD" as compared to true latent RHD including: > mild pathological valvular regurgitation at the mitral valve or aortic valve, mitral stenosis (mean MV gradient ≥ 5mmHg) (WHF classification: definite B), aortic stenosis (mean AV gradient ≥ 20mmHg).

3. Structural or functional cardiac defects, other than those consistent with RHD, that were known prior to or detected through echo screening (except patent foramen ovale, small atrial septal defect, small ventricular septal defect, small patent ductus arteriosus).
4. Self-report or prior allergic reaction to penicillin.
5. Any known conditions predisposing to thrombocytopenia or hypercoagulability, or other contraindications to intramuscular injection.
6. Any known co-morbid conditions (HIV, renal deficiencies, severe malnutrition, among others) that have resulted in prescription of regular antibiotic prophylaxis.

Study Duration

Four years

Investigational Medicinal Product

Oral phenoxymethyl penicillin (Pen V) prophylaxis 250mg twice daily.

Study Arms

Intervention Arm: Oral phenoxymethyl penicillin (Pen V) prophylaxis 250mg twice Daily.

Control Arm: Intramuscular Benzathine penicillin G (BPG). Children weighing 30 kg and above at date of administration will receive 1.2 million units (all 4ml of the injection) and those weighing less than 30kg will receive 600,000 units (2ml of the injection) via an intramuscular injection. BPG administration will occur at 4-week intervals for 26 4-week periods (24 months)

Sample size

1004 participants

Evaluator's Risk/Benefit Assessment:

The current information provided on the investigational product is sufficient to justify the proposed clinical trial. The potential benefits of conducting the trial are considered to outweigh the risks involved, provided that the study is carried out in accordance with the approved protocol, applicable local regulatory standards, ethical standards derived from the Declaration of Helsinki and the principles of Good Clinical Practice