| GOAL-Post | Statistical Analysis Plan |
|---|---|
| Version 1 – 2 July 2024 | |

# GOAL-Post

## A Long-Term Follow-up Study for Patients Who Participated in the GOAL Trial

## Determining the Impact of Penicillin on Latent Rheumatic Heart Disease

**Author**: Anneke Grobler, Murdoch Childrens Research Institute
**Date:** 2 July 2024

Based on protocol Version 1.3, dated 26 September 2021

**Document Version History**

| Version Date | Version | Author | Signature | Change Description | Reason/Comment |
|---|---|---|---|---|---|
| | | | | Initial release. | Not applicable. |
| | | | | | |
| | | | | | |

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| ARF | Acute Rheumatic fever |
| BPG | Benzathine Penicillin G |
| CI | Confidence interval |
| GOAL | GwokO Adunu pa Lutino ("protect the heart of a child") |
| GLM | Generalized Linear Model |
| RHD | Rheumatic Heart Disease |
| SAP | secondary antibiotic prophylaxis |
| WHF | World Heart Federation Criteria |

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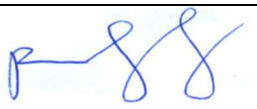
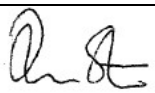
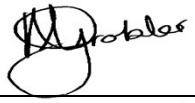
# 1. APPROVALS

The undersigned have reviewed this plan and approve it as final. They find it to be consistent with the requirements of the protocol as it applies to their respective areas. They also find it to be compliant with ICH-E9 principles and confirm that this analysis plan was developed in a completely blinded manner (i.e. without knowledge of the effect of the intervention being assessed)

| Name | Role on Study | Affiliation | Signature | Date |
|---|---|---|---|---|
| Andrea Beaton | Investigator | Cincinnati Children's Hospital |  | 07/2/2024 |
| Joselyn Rwebembera | Investigator | Uganda Heart Institute |  | 4th July 2024 |
| Andrew Steer | Investigator | Murdoch Children's Research Institute |  | 7th July 2024 |
| Anneke Grobler | Study statistician | Murdoch Children's Research Institute |  | 2 July 2024 |

# 2. STUDY OBJECTIVES

## 2.1. PRIMARY OBJECTIVE

To assess whether children who completed the GOAL (GwokO Adunu pa Lutino, "protect the heart of a child") Trial and now have normal echocardiograms have the same risk for progression as a new group of age and sex matched controls who have a normal echocardiogram at study entry.

**Aim 1:** Compare the two-year risk of echocardiographic progression between children and adolescents who completed the GOAL Trial with a normal echocardiogram (that is, a prior diagnosis of latent RHD) and age and sex matched controls with repeated normal echocardiograms (normal in both the original GOAL screening in 2017/2018 and in the GOAL-Post screening in 2021).

**Hypothesis**: The risk of RHD development (2012 World Heart Federation [WHF] Criteria) in children and adolescents who have had normalization of their echocardiogram following latent RHD diagnosis is not higher than children and adolescents without prior documentation of latent RHD.

**Clinical application***:* We are trying to answer the question: "Is it safe to take these children off Benzathine Penicillin G (BPG) after two years if they do not show latent RHD?"

## 2.2. SECONDARY OBJECTIVES

**Aim 2:** Determine the five-year rate of RHD progression and regression among children with persistent latent RHD who receive secondary antibiotic prophylaxis (SAP) - medium-term impact of prophylaxis. The five-year period includes time from initial GOAL enrollment to the end of GOAL-Post.

**Clinical application***:* We are trying to determine the durability of the intervention to prevent RHD progression.

**Additional aims (for participants with normal echocardiograms) (AIM 1):**
To assess the risk for RHD progression among children who completed the GOAL Trial and now have normal echocardiograms.

To assess the risk for progression among a new group of age/sex/geography matched controls who have a normal echocardiogram at study entry.

# 3. BACKGROUND/INTRODUCTION

The GOAL Trial reached completion in October 2020, finding that SAP resulted in a significant and substantial reduction in RHD progression among children with latent, or screen-detected RHD. These data have important clinical and public health implications. However, the GOAL Trial also showed that approximately 50% of children with latent RHD regressed at two-years, with the majority (85%) returning to a normal echocardiographic study with or without antibiotic prophylaxis. These results raise questions on the recommended duration of prophylaxis for latent RHD, with no current evidence to guide practice for this group.

GOAL-Post is two prospective extension studies that build on the infrastructure (case managers and peer groups) and success (98% retention and 99% BPG adherence) of the GOAL Trial.

## 3.1. STUDY DESIGN

GOAL-Post includes two observational studies to investigate outcomes for participants who completed the GOAL Trial, divided by final GOAL diagnosis: 1. *normal* or 2. *persistent latent RHD*. GOAL-Post will include former GOAL Trial participants (96% retention in care), as well as an age and sex matched cohort for Aim 1.

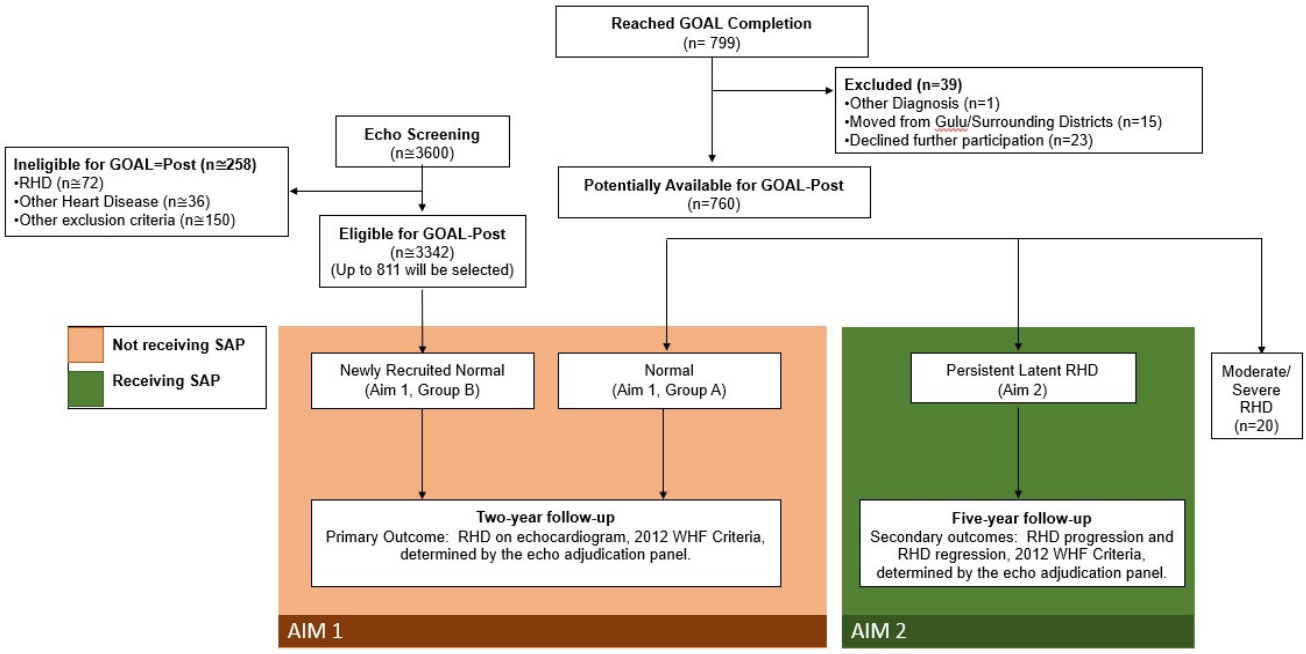



Figure 1: Design of GOAL-Post

### 3.2. TREATMENT GROUPS

The following treatment groups are identified within GOAL-Post:

- Never diagnosed with latent RHD (negative at screening for GOAL, and negative when screened for GOAL-Post) – Group 1B. This group has never received SAP.
- Randomized in the GOAL Trial to SAP and normal echocardiogram (no latent RHD) at the 2-year endpoint of the GOAL Trial and at the start of GOAL-Post. (Children who had SAP for two years and are then taken off SAP given a normal echocardiogram and no sign of latent RHD.)
- Randomized in the GOAL Trial to SAP and latent RHD at the start of GOAL-Post.
- Randomized in the GOAL Trial to control and normal echocardiogram (no latent RHD) at the 2-year endpoint of the GOAL Trial and at the start of GOAL-Post, these participants never received SAP.
- Randomized in the GOAL Trial to control and latent RHD at start of GOAL-Post. These participants did not receive SAP in the GOAL Trial but did receive SAP in GOAL-Post.

### 3.3. STUDY POPULATION

**Aim 1** planned to enrol between 953 and 1102 participants, a maximum of 364 participants with normal echocardiograms after 2-years of participation in the GOAL Trial (Group A) and an appropriate number of age and sex matched controls (Group B, see sample size) without echocardiographic evidence of RHD.

**Group A:** Children and adolescents were eligible for Aim 1 if they
(1) are a prior GOAL Trial participant deemed by the adjudication panel to have a normal echocardiogram at the 2-year endpoint,
(2) are not receiving SAP, and
(3) agree to participate in the study via the study's informed consent/assent process.

**Group B**: Children and adolescents were eligible for Aim 1 if they
(1) have a normal echocardiogram at the start of the study,
(2) meet the age and sex match requirement (from former GOAL Trial participants), and
(3) have agreed to participate in the study via the study's informed consent/assent process.

**Aim 2** planned to enrol up to 415 participants with persistent latent RHD after 2 years of participation in the GOAL Trial. Children and adolescents were eligible for Aim 2 if they
(1) were a prior GOAL Trial participant deemed by the adjudication panel to have persistent latent RHD on echocardiogram at the 2-year endpoint,
(2) have been prescribed SAP (BPG), and
(3) agree to participate in the study via the study's informed consent/assent process.

### 3.4. SAMPLE SIZE

**Aim 1:** A sample size of between 953 and 1102 participants (up to 350 and as few as 291 participants with normal echocardiograms after the GOAL Trial and up to 811 age and sex matched controls) will be needed, assuming up to 10% loss to follow-up and that 2% of the control group (Group B), and 3% of the children who completed the GOAL Trial (Group A) will develop RHD.

A two-group large-sample normal approximation test of proportions with a one-sided 2.5% significance level will have 80% power to reject the null hypothesis of a difference in proportions of <2% in favor of the alternate hypothesis that the proportion of the two groups are equivalent. Calculation was done using nQuery 8 (Statistical Solutions Ltd). This sample size was increased by 10% to account for loss to follow-up.

**Aim 2** does not include a comparator group and will include the maximum number of former GOAL Trial participants with persistent latent RHD (currently 415 retained in care).

For Aim 1 Group A we plan to enrol all the participants who were enrolled in the GOAL Trial, meet the eligibility criteria and are willing to be enrolled in the GOAL-Post extension study. The maximum number that can be enrolled in group A is 364 who had normal echocardiograms at the end of the GOAL Trial. If this maximum number is enrolled, and there is 10% loss to follow-up in GOAL-Post, we need to enrol 589 participants in Group B. This gives a total sample size of 953.

Since there is only a fixed number of children who qualify for enrolment into Group A, we determined the size of Group B after group A has been enrolled. The size of Group B was determined to give 80% power, given the size of Group A, under the previous assumptions. The smallest sample size for Group B is given above. If 90% of the original cohort are enrolled in Group A, the size of Group A will be 328 and the size of Group B will be 666 for a total sample size of 994. If only 80% of the original cohort are enrolled in Group A, the size of Group A will be 291 and the size of Group B will be 811 for a total sample size of 1102.

### 3.5. STUDY PROCEDURE

**Table 1: Aim 1 GOAL-Post Assessment Schedule**

| | **Enroll** | **Year 1 Follow-up** | | | | **Year 2 Follow-up** | | | | **Final Visit** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | **Q0** | **Q1** | **Q2** | **Q3** | **Q4** | **Q5** | **Q6** | **Q7** | **Q8** | |
| Informed Consent/Assent | X | | | | | | | | | |
| Demographics | X* | | | | | | | | | |
| Medical History | X* | | | | | | | | | |
| Family History | X* | | | | | | | | | |
| Concomitant Healthcare | | X | | X | | X | | X | | X |
| Echocardiogram | X** | | | | X | | | | | X |
| *Only Aim 1, Group B as these data are already collected for former GOAL Trial participants<br>** Will use GOAL end of trial echocardiogram for Aim 1, Group A and obtain a full echocardiogram for Aim 1, Group B participants during the enrollment visit. | | | | | | | | | | |

**Table 2: Aim 2 GOAL-Post Assessment Schedule**

| | **Transitional Year (Year 3 follow-up)** | | | | **GOAL-Post Year 1 (Year 4 follow-up)** | | | | **GOAL-Post Year 2 (Year 5 follow-up)** | | | | **Final Visit** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | **Q1** | **Q2** | **Q3** | **Q4** | **Q5** | **Q6** | **Q7** | **Q8** | **Q9** | **Q10** | **Q11** | **Q12** | |
| Informed Consent/Assent | X | | | | X | | | | | | | | |
| Concomitant Healthcare | X | | X | | X | | X | | X | | X | | X |
| BPG Diary | X | X | X | X | X | X | X | X | X | X | X | X | |
| Adverse Events | X | X | X | X | X | X | X | X | X | X | X | X | |
| Echocardiogram | X* | | | | X | | | | X | | | | X |
| * GOAL end of trial echocardiogram. | | | | | | | | | | | | | |

## 4. POPULATIONS OF ANALYSIS

For **Aim 1** the analysis population will be all participants enrolled in Aim 1 in GOAL-Post. The Aim 1 Group A population is defined as GOAL-Post consent completed, arm 1 selected, and GOAL-Post enrolment echo is normal. The Aim 1 Group B population is defined as GOAL-Post consent completed and arm 4 selected.

For **Aim 2** the analysis population will be all participants enrolled in Aim 2 in GOAL-Post. The Aim 2 population is defined as GOAL-Post consent completed and arm 2 selected, or GOAL-Post consent completed, arm 1 selected, and GOAL-Post enrolment echo is not normal.

## 5. OUTCOME VARIABLES

All Aim 1 echocardiograms will undergo blinded review by a panel of 2 cardiologists (2012 WHF guidelines), consisting of pre-review by 2 of these cardiologists (to guide discussion) and final consensus determination by the panel. A side-by-side comparison of the echo done at the end of the GOAL Trial and the end of GOAL-Post will also be done. Echocardiograms will be reviewed with side-by-side two-year (completion of the GOAL Trial) and five-year (end of GOAL-Post) echocardiograms presented to the panel, with random right or left display. The panel will be blinded to timing of the echocardiograms and will determine if the studies were "the same", "right worse" or "left worse" by application of strict operational definitions, defined in the GOAL Trial.

The primary outcome of **Aim 1** will be development of echocardiographic evidence of RHD (2012 WHF Criteria) among children and adolescents with a normal echocardiogram at the 2-year endpoint in the GOAL Trial and upon enrolment into GOAL-Post (variable enollecho).

**An alternative outcome** for **Aim 1** is worsening on a side-by-side comparison of the echo done at the end of the GOAL Trial and the end of the GOAL-Post trial. These will be assessed as same, progressed or regressed. This is done only for Group A. This is captured in the database as a combination of two variables. If eligible_echo_comparison is "no" then the result is "same". If eligible_echo_comparison is "yes" then the result is captured in the variable side_by_side results. The final diagnosis is given as the variable final_diagnosis_after_comparison. Again this variable is a combination of two variables . If eligible_echo_comparison is "no" then the result is "normal".

The primary outcome of **Aim 2** will be echocardiographic progression and regression among children who had persistent latent RHD at the end of the GOAL Trial. This will be variable enollecho from Period 26.

Progression is defined as progression of echocardiographic features of latent RHD to include:

- New pathological regurgitation at a previously unaffected valve
- Worsening grade of existing mitral or aortic regurgitation (mild, moderate, severe)
- Development of two morphological features consistent with RHD (2012 WHF criteria) 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.

In all cases progression will involve a change in diagnostic category (borderline to definite mild, or definite mild to definite moderate/severe).

Regression will be defined as regression of echocardiographic features of latent RHD to include:

- Disappearance of existing mitral or aortic regurgitation, or change from pathological regurgitation to physiological regurgitation (2012 WHF criteria)
- Decreasing grade of existing mitral or aortic regurgitation (trivial, none)
- Disappearance of a morphological feature consistent with RHD (2012 WHF criteria) at a valve that previously had abnormal morphology.

In all cases, regression will involve a change in diagnostic category (borderline to normal, or definite to borderline/normal).

# 6. STATISTICAL METHODOLOGY

## 6.1. AIM 1 PRIMARY ANALYSES

We will report the proportion of children who develop echocardiographic evidence of RHD in each of Group A and B (never diagnosed with latent RHD; negative at screening for GOAL, and negative when screened for GOAL-Post). We will fit a generalized linear model (GLM) with an identity link and binomial distribution, adjusted for the matching factors age and sex to estimate the difference in proportion of children who develop echocardiographic evidence of RHD, with a 95% confidence interval (CI), between Groups A and B.

To assess whether this difference in proportion between the two groups is < 2% we will evaluate the upper bound of the estimated 2-sided 95% CI for the difference in proportions calculated from the GLM. If this CI does not include a difference larger than 2%, the risk for development of RHD will be assessed to be similar in the two groups of participants.

Children with confirmed Acute Rheumatic fever (ARF) and children who develop echocardiographic evidence of RHD prior to the 2-year endpoint will be counted as having reached the primary study endpoint (development of RHD).

We will also repeat the analysis, using the same statistical methods, but restricting the analysis to only the subgroup of children who were randomized to the BPG arm in the GOAL Trial. This will reduce the sample size and power, therefore we do not expect to be powered to show statistically significant results, but will provide all estimates to serve for hypothesis generation.

The results of the side-by-side comparison of echocardiograms will be summarized.

## 6.2. AIM 1 EXPLORATORY ANALYSIS

An exploratory analysis will compare risk between participants in Aim 1, Group A who did and did not receive SAP (BPG) during the GOAL Trial. In order to do this comparison, we will “reconstruct” or emulate a longer trial, in essence analysing the data as if the GOAL Trial originally had longer follow-up planned. This will follow the framework of target trial emulation for the design and analysis of observational studies that involves precisely specifying the protocol of the target trial and then emulating each component of the protocol with observational data (1).

Our target trial (which we will call the **Target-GOAL Trial**) would have randomized participants to the following groups at the start of the GOAL Trial. Each group represents a treatment algorithm, with a predetermined change at 2 years based on the results of an echocardiogram done at 2 years (in our case, at the end of the GOAL-Trial).

Randomized groups at the start of the Target-GOAL Trial:

- Treat with BPG for 2 years. Assess with echocardiogram after 2 years. If normal at the end of 2 years, stop treatment. If latent disease is present then treat with BPG for 3 years.
- Do not treat with BPG for 2 years. Assess with echocardiogram after 2 years. If normal at the end of 2 years no change. If latent disease is present then treat with BPG.

| Randomized at the start of the GOAL Trial to one of the following interventions | 2 years post randomization Echocardiogram done – RHD status assessed | | Intervention for 3 years | 5 years after randomization Echocardiogram done – RHD status assessed |
| --- | --- | --- | --- | --- |
| BPG | - Normal | → | No treatment | |
| | - Latent RHD | → | Treat with BPG | Outcome |
| | - Severe | → | Outcome: RHD | |
| Control | - Normal | → | No treatment | |
| | - Latent RHD | → | Treat with BPG | Outcome |
| | - Severe | → | Outcome: RHD | |

**Figure 2: Groups randomized to at the start if the Target-GOAL Trial**

This study design answers, from a randomized comparison, the following question: What is the impact of treatment with BPG for 2 years, after which participants with a normal echocardiogram stop treatment, and participants with latent RHD start treatment, compared to no treatment in the initial 2 years, 5 years after initial diagnosis of latent RHD.

The primary study outcome is development of RHD on the side by side comparison. Participants with confirmed ARF and who develop echocardiographic evidence of RHD at any time during the study period will be counted as having reached the primary study endpoint (development of RHD).

We will report the proportion of children who develop echocardiographic evidence of RHD in each of the "randomized" groups in Target-GOAL. We will fit a GLM with an identity link and binomial distribution, adjusted for stratification variables in GOAL (RHD category borderline or definite), to estimate the difference in proportion of children who develop echocardiographic evidence of RHD, with a 95% CI, between the two "randomized" arms.

We will also report the proportion of participants with RHD in each of the following groups:

- SAP for 2 years, no latent RHD, no treatment
- SAP for 2 years, latent RHD, SAP
- Control for 2 years, no latent RHD, no treatment
- Control for 2 years, latent RHD, SAP

Given that there will be a larger proportion of missing data for this Target-GOAL trial, we will do the analysis with all the data we have (available case analysis) and also repeat the analysis using multiple imputation to adjust for the missing outcome data. We will assume that the missing data is missing at random. We will use the Multiple Imputation by Chained Equations (MICE) method using a Gibbs-like algorithm to impute multiple variables sequentially using univariate fully conditional specifications. We will include the outcome variable, treatment arm, stratification variable and appropriate baseline variables from the GOAL trial in the imputation model.

### 6.3. AIM 2

We will determine the proportion of children with RHD progression and regression at 5 years among children with persistent latent RHD who receive every-4-week BPG prophylaxis and present this proportion with a

95% CI interval. An exploratory sub-analysis will compare risk between participants in Aim 2 who did and did not receive SAP during the GOAL Trial.

We will calculate the rate of progression and regression at the end of GOAL-Post in the following groups of participants:

- Randomized in the GOAL Trial to SAP and latent RHD at the start of GOAL-Post.
- Randomized in the GOAL Trial to control and latent RHD at start of GOAL-Post. These participants did not receive SAP in the GOAL Trial but did receive SAP in GOAL-Post.

Additional

- Randomized in the GOAL Trial to SAP and normal echocardiogram (no latent RHD) at the 2-year endpoint of the GOAL Trial and at the start of GOAL-Post. (Children who had SAP for two years and are then taken off SAP given a normal echocardiogram and no sign of latent RHD.)
- Randomized in the GOAL Trial to control and normal echocardiogram (no latent RHD) at the 2-year endpoint of the GOAL Trial and at the start of GOAL-Post, these participants never received SAP.
- Normal at the end of the GOAL Trial, regardless of randomized treatment arm

## 7. REFERENCE LIST

1. Hernán MA, Wang W, Leaf DE. Target Trial Emulation: A Framework for Causal Inference From Observational Data. JAMA. 2022;328(24):2446-7.

## 8. LIST OF TABLES, FIGURES AND LISTINGS

**Table 1: Demographics in Aim 1**

| Demographic variables | Group A | Group B |
| --- | --- | --- |
| Age | | |
| Sex | | |
| Etc. | | |

**Table 2: Demographics in Aim 2**

| Demographic variables | BPG + | Control + | Aim 2 in GOAL-Post |
| --- | --- | --- | --- |
| Age | | | |
| Sex | | | |
| Etc. | | | |

**Table 3: Aim 1 primary analysis**

| | Proportion with RHD | | | |
| --- | --- | --- | --- | --- |
| **Evidence of RHD** | **Group A Proportion (95% CI)** | **Group B Proportion (95% CI)** | **Difference (95% CI)** | **p-value** |
| All participants in Aim 1 | | | | |
| Only participants randomized to the BPG arm in the GOAL Trial | | | | |
| **Using side by side comparison** | | | | |
| All participants in Aim 1 | | | | |
| Only participants randomized to the BPG arm in the GOAL Trial | | | | |

Group A: Children who completed the GOAL Trial and have normal echocardiograms in GOAL-Post
Group B: A new group of age and sex matched controls who have normal echocardiogram at study entry

**Table 4: Proportion with progression and regression in Group A**

| | Proportion (95% CI) |
| --- | --- |
| **Proportion worsened (progressed)** | |
| All participants in Aim 1 | |
| Only participants randomized to the BPG arm in the GOAL Trial | |
| **Proportion better (regressed)** | |
| All participants in Aim 1 | |
| Only participants randomized to the BPG arm in the GOAL Trial | |

Group A: Children who completed the GOAL Trial and have normal echocardiograms in GOAL-Post

**Table 5: Proportion of participants with RHD**

| Group | Proportion (95% CI) |
| --- | --- |
| Randomized in the GOAL Trial to SAP and normal echocardiogram (no latent RHD) at the 2-year endpoint of the GOAL Trial and at the start of GOAL-Post. (Children who had SAP for two years and are then taken off SAP given a normal echocardiogram and no sign of latent RHD.) | |
| Never diagnosed with latent RHD (negative at screening for GOAL, and negative when screened for GOAL-Post) – Group 1B. This group has never received SAP. | |
| Randomized in the GOAL Trial to SAP and latent RHD at the start of GOAL-Post. | |
| Randomized in the GOAL Trial to control and normal echocardiogram (no latent RHD) at the 2-year endpoint of the GOAL Trial and at the start of GOAL-Post, these participants never received SAP. | |
| Randomized in the GOAL Trial to control and latent RHD at start of GOAL-Post. These participants did not receive SAP in the GOAL Trial but did receive SAP in GOAL-Post. | |
| Normal at the end of the GOAL Trial, regardless of randomized treatment arm | |

**Table 6: Primary outcome of Target-GOAL Trial (Progression on side by side echo)**

| | BPG +<br>Proportion (95% CI) | Control +<br>Proportion (95% CI) | Difference<br>(95% CI) | p-value |
| --- | --- | --- | --- | --- |
| Available case analysis | | | | |
| Analysis using multiple imputation | | | | |

BPG +: Treat with BPG for 2 years. Assess with echocardiogram after 2 years. If normal at the end of 2 years, stop treatment. If latent disease is present then treat with BPG for an additional 3 years.
Control +: Do not treat with BPG for 2 years. Assess with echocardiogram after 2 years. If normal at the end of 2 years no change. If latent disease is present then treat with BPG for 3 years.

**Table 7: Aim 2: Proportion of participants with progression and regression at 5 years**

| | Progression (95% CI) | Regression (95% CI) |
| --- | --- | --- |
| Participants with persistent RHD at start of GOAL-Post | | |
| Participants with persistent RHD at start of GOAL-Post who received BPG in GOAL | | |
| Participants with persistent RHD at start of GOAL-Post who received control in GOAL | | |
| Compare risk between participants in Aim 2 who did and did not receive SAP during the GOAL Trial. | Risk difference and p-value for progression between previous two lines | |
| Randomized in the GOAL Trial to SAP and latent RHD at the start of GOAL-Post. | | |
| Randomized in the GOAL Trial to control and latent RHD at start of GOAL-Post. These participants did not receive SAP in the GOAL Trial but did receive SAP in GOAL-Post. | | |
| Latent RHD at the start of GOAL-Post, regardless of randomization in GOAL Trial | | |
| **Additional** | | |
| Randomized in the GOAL Trial to SAP and normal echocardiogram (no latent RHD) at the 2-year endpoint of the GOAL Trial and at the start of GOAL-Post. (Children who had SAP for two years and are then taken off SAP given a normal echocardiogram and no sign of latent RHD.) | | |
| Randomized in the GOAL Trial to control and normal echocardiogram (no latent RHD) at the 2-year endpoint of the GOAL Trial and at the start of GOAL-Post, these participants never received SAP. | | |
| Normal at the end of the GOAL Trial, regardless of randomized treatment arm | | |