Clinical characteristics and outcomes of children with Rheumatic Heart Disease: A Global Rheumatic Heart Disease Registry (REMEDY) sub-analysis

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Declaration Page

The work presented in this dissertation has been based on independent research (unless otherwise stated and referenced) and has not been submitted for another degree with any other university. This research has not been published or reported prior to my registration for the abovementioned degree. The University of Cape Town is authorized to reproduce the whole or any part of this work for the purpose of research.

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22 August 2020

Abstract

Background:

Acute Rheumatic Fever (ARF) and its sequel Rheumatic Heart Disease (RHD), contributed to an estimated disease burden of 40 million people in 2017 with over 285 500 deaths. We present a sub-analysis of children from the multi-centre prospective two year Global Rheumatic Heart Disease Registry (REMEDY) study.

Methods:

We performed a sub-analysis of the patients below 19 years with symptomatic RHD enrolled in the REMEDY registry at the baseline visit and followed up at 12 months and 24 months.

Results:

More than half of the children enrolled in the REMEDY study presented with severe valvular heart disease; 60% had more than one valve involved, 30% were classified as NYHA class III/IV and 17.7% died within 24 months. Just over 20% of children were not on penicillin prophylaxis. Although 20% met criteria for surgery, only less than 9% (n=78, 8.5%) had had percutaneous or surgical intervention with half from upper-middle-income countries. The major risk factors associated with mortality included older age (Hazard Ratio (HR): 1.01, p=0.001) and atrial fibrillation or flutter (HR: 2.3, p=0.028). Female gender (HR: 0.68, p=0.062) and education level above primary school (HR: 0.88, p=0.68) did not confer significant protection. However, a past medical history of ARF conferred some protection against mortality (HR: 0.61, p=0.031). In follow-up, 30% (n=238, 29.6%) of children experienced an adverse cardiovascular event, nearly 15% (n=114, 14.1%) were hospitalised and six young women became pregnant during the study period.

Conclusion:

Children with RHD in low- and middle-income countries are severely affected and have limited access to surgical treatment despite significant morbidity and mortality.

Acknowledgments and Contributions

I would like to thank my supervisor Professor Liesl Zühlke for her great support, teaching, and guidance throughout the process of this dissertation and the great patience she displayed with me. Greatly appreciate the REMEDY study board who granted permission to allow a sub-analysis of their original work resulting in this research project. As well as the great patience and tutelage rendered to me by Susan Perkins from the Children's Heart Disease Research Unit at Red Cross War Memorial Children's Hospital and Professor Mark E Engel. Acknowledging, also, the support from my family and friends during this time.

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List of Abbreviations and Acronyms

AHA/ACC	America Heart Association and the American College of Cardiology
AIIMS	All India Institutes of Medical Sciences
ARF	Acute Rheumatic Fever
A.S.A.P.	Awareness, Surveillance, Advocacy and Prevention
CRF	Case Report Form
CRP	C-Reactive Proteins
CNS	Central Nervous System
DALYs	Disability Adjusted Life Years
ECG	Electrocardiogram
Echo	Echocardiogram
ESR	Erythrocyte Sedimentation Rate
GAS	Group A Streptococcus
GBD	Global burden of disease
HR	Hazard Ratio
HLA	Human Leukocyte Antigen
LICs	Lower Income Countries
LMICs	Low- and Middle-Income Countries
MR	Mitral regurgitation
NCD	Non-Communicable Disease
NYHA	New York Heart Association
NSAID	Nonsteroidal anti-inflammatory drug
PASCAR	Pan African Society of Cardiology
PR	P-R interval
REMEDY	Global Rheumatic Heart Disease Registry
RHD	Rheumatic Heart Disease
SDGs	Sustainable Developmental Goals
THESUS-HF	The sub-Saharan Survey of Heart Failure
UMICs	Upper-Middle Income Countries
VALVAFRIC	Western and Central African RHD registry
WHA	World Health Assembly
WHF	World Heart Federation
WHO	World Health Organization

Chapter 1: Introduction and Literature Review

Rheumatic Heart Disease (RHD) is the sequel to Acute Rheumatic Fever (ARF) following a Group A streptococcus (GAS) Infection. This chronic heart disease is totally preventable if the GAS infection is treated, but, due to late presentation, under-recognition and under-treatment, carries significant mortality and morbidity among children and adults. RHD and its precursor, ARF, have a distinct clinical course which usually begins in childhood, progresses through adolescence and presents with secondary complications and mortality in early adulthood or in the peri-partum period, a particular risk factor.

Despite great strides in well-resourced countries that resulted in the reduction of the prevalence and age-standardized mortality of RHD by 21,3% from 2007 to 2017, communities in under-resourced settings and indigenous people in high-income countries such as Australia and New Zealand still face an almost insurmountable battle with RHD [1]. Over the past decades, RHD has been a neglected non-communicable disease (NCD) despite its high burden with a poor reflection on associated public health issues such as access to care, leaving the disenfranchised and poorly-resourced communities to manage its deleterious effects.

A remarkable resurgence in research into the global prevalence of RHD has occurred, including prevalence studies for asymptomatic RHD using echocardiography and the revision of the diagnostic criteria for ARF, accompanied by public policy and advocacy, largely from areas of the world where RHD is endemic[2-4]. Medical experts have sought to reinvigorate the world with regards to RHD awareness and accelerate public efforts to eliminate ARF/RHD.[5] There has been a drive to newer and more contemporary research including comprehensive data and registries of patients living with RHD in these low-resourced parts of the world [6-8] .These have also resulted in major public health policy gains. In 2016, the Addis Ababa communiqué was adopted by the African Union (AU) and more recently in 2018, at the 71st World Health Assembly (WHA), a landmark resolution (71.14) against ARF/RHD was passed [5, 9]. Within both these historic documents is a blueprint of interventions including scientific, community and collaborative approaches to eliminate, eradicate and control this disease.

This chapter is a comprehensive review of the literature on the epidemiology, burden, pathogenesis, diagnosis and treatment of RHD as well as global policies needed to address the prevention and control of ARF and RHD for vulnerable populations.

The literature for this review was gathered from the following sources: Pubmed, Medline, Google Scholar and the University of Cape Town online Library. Key words

used for searching included *acute rheumatic fever, rheumatic heart disease,* combined with *incidence, global prevalence, pathogenesis, children, management and registries.* Other key phrases included *acquired heart disease, Africa* and *valvular heart disease.* The literature search yielded 30 studies, 19 review articles and 3 guideline papers.

Acute Rheumatic Fever

Acute Rheumatic Fever is a systemic auto-inflammatory disease that appears within two to four weeks following an episode of pharyngitis caused by Group A streptococcus. GAS is one of the leading causes of bacterial pharyngitis and the most common reason for sore throat [10].This type of pharyngitis is usually found in those aged 5 to 15 years and is less common in those over 30 years old. The global pattern of incidence and prevalence of ARF is varied with the highest burden still seen in countries with a lower socio-economic standing, while developed countries have seen a decline. A systematic review of the overall burden of ARF showed a mean incidence of first attack to be 5-15 per 100 000 population (mean: 19 per 100 000, 95% confidence interval: 9 to 30 per 100 000). The lowest incidence is seen in America and Western Europe and a higher incidence in Eastern Europe, the Middle East, Asia and Australia. No results were included from Africa in this review due to lack of studies for ARF [11].

Countries with wide socio-economic disparities also show within-country variations in burden. An example of this is Australia with the highest incidence of ARF in those between the ages of 5 and 14 years at 194 per 100 000 population [12, 13].These cases are mostly seen in the indigenous Aboriginal people who also live in areas where poverty is rampant, housing is poor and access to health care is limited. Meanwhile, urban areas of Australia exhibit a more Western pattern with lower ARF incidences [14].Another burden of distribution is seen in developing countries with improving socio-economic conditions and those experiencing rapid urbanization like India, which has seen a decline in ARF and RHD incidence rates ([15].

The relatively few population-based studies on the overall prevalence of RHD in Africa indicates the continent as having some of the highest burden of RHD in the world, as illustrated by Watkins et al.'s (2015) Global Burden of Disease Survey of 1990 to 2015. Difficulties in health access and poor health-seeking behaviour contribute to difficulties in diagnosing ARF, treating it and giving secondary prophylaxis to reduce the burden of RHD [2].

GAS not only causes ARF but can also lead to skin infections such as impetigo and renal sequalae as in the case of post-streptococcal glomerulonephritis. Newer research has suggested that impetigo could be linked to ARF as higher numbers of GAS skin infections are seen in ARF endemic areas than GAS pharyngitis. The global GAS

prevalence is estimated to be about 18 million cases with 1,78 million cases per year [16].Overcrowding and poor social circumstances are the greatest risk factors to developing GAS infections, and hence ARF.

The Pathogenesis of ARF

ARF results from an autoimmune response to infection with GAS in genetically predisposed host [17]. There are two theories regarding the pathogenesis of ARF following GAS infection, namely the "molecular mimicry theory" and the "neo-antigen theory". The former is based on the structural molecular similarity between the GAS antigen and the heart actin and myosin structures, leading to cross-reactivity with the antibodies against the antigen and subsequent formation of autoantibodies. This then results in damage to the heart muscle fibers. The newer neo-antigen theory states that the GAS organism gains access to the subendothelial collagen matrix of the heart, M-proteins of the antigen then binds to the CB3 region of the type IV collagen leading to the formation of a "neo-antigen" that causes an autoimmune response against the collagen fibers. This then triggers an inflammatory cascade that results in neovascularization and fibrosis with repeated episodes of ARF causing permanent heart valve damage [18, 19].

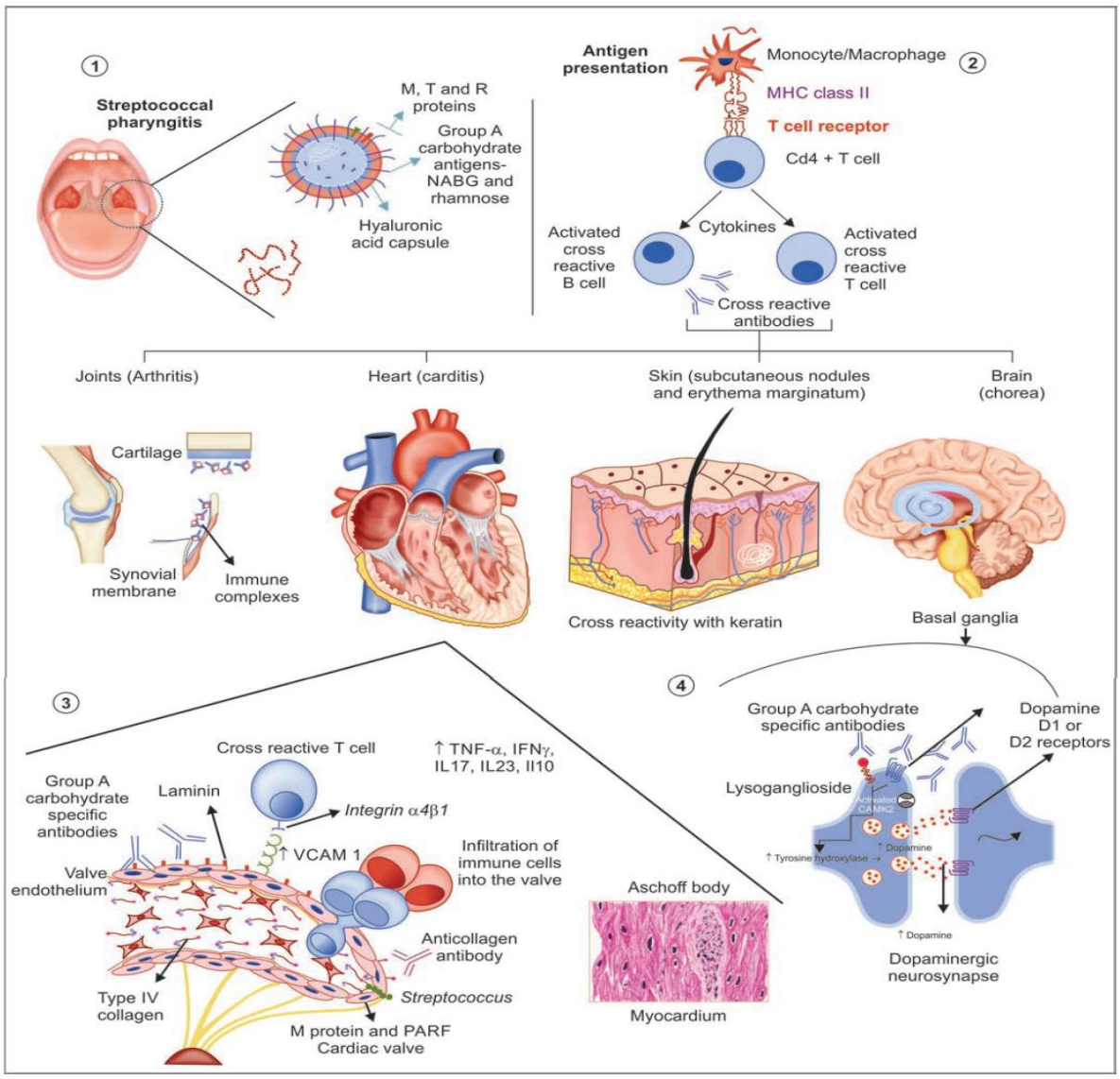
Widespread endothelial inflammation has been attributed to the systemic manifestation of ARF. Skin endothelial inflammation leading to evanescent erythema marginatum and self-limiting subendothelial nodules, synovial endothelial inflammation leading to arthritis and CNS endothelial involvement with chorea [20].There is also a wide variation in the M-protein type distribution globally, with different strains and antigens causing ARF in different parts of the world. In New Zealand, 74 strains of GAS were seen to be associated with ARF and a subtyping of the GAS strains according to N terminus of the M-protein showed more than 200 emm-types [18].This is still an area needing further research with regards to the causative antigens, their virulence and their epidemiology.

Since the risk of developing ARF following GAS pharyngitis is estimated at about 0,3 to 3%, genetic host-predisposing factors such as class II major histocompatibility antigens or human leukocyte antigen (HLA) and D8/17 B-cell alloantigens have been investigated as either protective or increasing the risk for developing ARF [21]. It has been noted that the cumulative incidence of ARF remains unchanged in areas where there is an outbreak of a rheumatogenic strain of GAS. Considering that a family history of ARF is sometimes present in those who develop it, the genetic susceptibility to ARF in other individuals has been considered.

Bryant et al. published a review in 2009 looking at hereditary susceptibility of ARF [22] .Studies of HLA subtypes suggested that HLA class II molecules are associated with an

increased risk of being susceptible to ARF, especially in those with cardiac manifestations. The authors also found that B-cell alloantigens and polymorphisms in the promoter region of immune cell genes such as tumor necrosis factor alpha genes to be increased in those with ARF. However, it may be that these are not disease makers but rather host genetic predisposing factors; further research in this area is clearly indicated [22].Developing ARF is a complex interplay of three factors: 1) infection with a rheumatogenic strain of group A streptococcus, 2) a genetically susceptible individual and 3) an aberrant host immune response [17].Evidence of the specific genetic factors involved in the pathogenesis and their expression is still sparse and studies continue to review the genome of the ARF-susceptible population compared to the non-susceptible population, in order to answer the many questions that remain [17] .

Figure 1 illustrates the pathogenesis of ARF from initial streptococcal pharyngitis infection to the resulting impact on the skin, heart, brain and joints [23].



Pathogenesis of rheumatic fever. **1.** GAS pharyngitis leads to antigenic presentation of pathogenic peptides to T-cells. **2.** In immunologically susceptible individuals, the innate and adaptive (both humoral and cellular) immune responses gets activated leading to the development of cross-reactive antibodies and cross-reactive T-cells which incites immune response in the joints, heart, skin, and brain leading to different manifestations of ARF. **3.** In the heart, valve damage is initiated by 'endothelial activation' by cross-reactive antibodies which trigger increased expression of vascular cell adhesion molecule-1 (VCAM-1). This facilitates T-cell infiltration leading to cytokine-mediated immune damage. Exposure of Type-IV collagen can lead to production of collagen-specific antibodies which can cause further damage. **4.** In the brain, autoantibodies can target dopamine receptors and lysoganglioside leading to increased release of dopamine by the neurons thereby causing rheumatic chorea

Abbreviations: ARF, acute rheumatic fever; GAS, group A *Streptococcus*; IL, interleukin; IFN, interferon; NABG, N-acetyl-β-d-glucosamine; PARF, peptide associated with rheumatic fever; TNF, tumor necrosis factor; VCAM-1, vascular cell adhesion molecule-1

Source : Essentials of Postgraduate Cardiology 2018

Figure 1: The pathogenesis of rheumatic fever [23]

Diagnosis of ARF

The clinical picture of ARF usually involves the patient presenting with fever, painful large joints often in a migrating fashion, and poor effort intolerance or heart failure, following a history of sore throat 2-3 weeks prior. Poor effort intolerance is indicative of carditis, which presents as a new systolic murmur on auscultation, subclinical carditis on echocardiography or in severe cases, overt heart failure [15]) .

The Jones Criteria incorporates specific clinical features into criteria for the diagnosis of ARF. It was first developed in 1944 and later modified in 1965, 1984, 1992, 2002, and most recently revised in 2015 [4, 24].It includes evidence of a prior GAS infection denoted by a high or rising titre of GAS antibodies (anti-streptolysin O titer or antideoxyribonuclease-B antibody), a positive throat swab or, in countries where this is performed, a positive rapid antigen test. The major Jones Criteria are carditis, arthritis, chorea, erythema marginatum and subcutaneous nodules. The minor criteria include fever, raised inflammatory markers, joint pain and a prolonged PR interval on electrocardiogram (ECG) (see Table 1).

The Revised Jones Criteria, published in association with the World Heart Federation (WHF) in 2015, were reviewed to improve the diagnosis of ARF in the context of global variation in the risk to populations (endemic vs non endemic areas) and improved recognition of subclinical carditis – carditis diagnosed on echocardiography alone. Population groups with an ARF incidence of <2 per 100 000 school-aged children per year and an all-age RHD prevalence of less than or equal to 1 per 1000 are considered low-risk [4].

Subclinical carditis can be found on echocardiogram (echo) with features suggestive of valvulitis, more commonly the mitral and aortic valves with regurgitation. It can also be diagnosed clinically by auscultation of a new or changing systolic murmur. Echocardiography should be performed in cases of suspected and confirmed ARF. Once diagnosed with ARF, serial echos should be performed regardless of an initial confirmation of present/absent carditis to monitor progression or regression. Doppler findings should be consistent with the rheumatic features of carditis and exclude other causes of heart murmurs by fulfilling all four criteria of pathological valvulitis or morphological abnormalities [25] .

Arthritis is of a migratory nature (typically affecting the major joints such as the wrists, elbows, knees and ankles in succession) and is usually the earliest sign of ARF, especially in adolescents and young adults compared to children ([15]. Polyarthralgia has now been included as a major manifestation in moderate- to high-risk populations after exclusion of other common causes of arthralgia [4, 15].

Sydenham's Chorea (also known as St. Vitus dance) is a later presentation of GAS infection at about 1 to 8 months following the initial infection. Therefore, it may not be observed at the time of ARF diagnosis. It is more prevalent in young girls and may present as subtly as changes in personality or display of social withdrawal symptoms. Clinically it can present as sudden and abrupt movement of the limbs that can be fine or gross as well, with decreased muscle tone and weakness. No sensory loss or pyramidal tract involvement can be demonstrated on central nervous system (CNS)

exam. Chorea usually resolves in around 6 weeks to 6 months, but severe cases may require treatment with immunomodulating medication and anti-movement disorder medication [15].

Erythema marginatum is a round, snake-like rash with red margins and clearing centrally. It is more commonly found on the trunk and limbs and can appear and disappear within hours but can reportedly be made more pronounced by hot baths. It is typically a non-pruritic rash and usually presents earlier in the natural history of ARF. Subcutaneous nodules are found on the extensor surfaces of joints over tendons. They are usually non-tender with normal overlying skin and can be as large as 2 cm. They are found in the acute phase of the disease and can be associated with severe carditis. The nodules are self-limiting and usually disappear within a month. Subcutaneous nodules are not a common finding in those with ARF and seldom occur as a single major manifestation of it [4, 15] .

Fever associated with ARF is usually higher than 38,5 degrees Celsius, but any fever higher than 38 should be considered a minor criterion in high-risk populations. Joint pain, without signs of arthritis, is also included as a minor criterion. Raised acute phase reactants like erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are included in the minor criteria, and at different levels according to the population risk group [4].

Interpreting PR interval prolongation on the ECG depends on the age group of the presenting patient. A prolonged PR interval is a minor criterion, but ARF can also present with a second-degree or a complete third-degree heart block [4, 18].

Table 1: The Revised Jones Criteria, adapted from Gewits et al [4].

A. For all patient populations with evidence of preceding GAS infection	
Diagnosis: initial ARF	2 Major manifestations or 1 major plus 2 minor manifestations
Diagnosis: recurrent ARF	2 Major or 1 major and 2 minor or 3 minor
B. Major criteria	
Low-risk populations*	Moderate- and high-risk populations
Carditis† • Clinical and/or subclinical	Carditis • Clinical and/or subclinical
Arthritis • Polyarthritis only	Arthritis • Monoarthritis or polyarthritis • Polyarthralgia‡
Chorea	Chorea
Erythema marginatum	Erythema marginatum
Subcutaneous nodules	Subcutaneous nodules
C. Minor criteria	
Low-risk populations*	Moderate- and high-risk populations
Polyarthralgia	Monoarthralgia
Fever (≥38.5°C)	Fever (≥38°C)
ESR ≥60 mm in the first hour and/or CRP ≥3.0 mg/dL§	ESR ≥30 mm/h and/or CRP ≥3.0 mg/dL§
Prolonged PR interval, after accounting for age variability (unless carditis is a major criterion)	Prolonged PR interval, after accounting for age variability (unless carditis is a major criterion)

ARF indicates acute rheumatic fever; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; and GAS, group A streptococcal infection.

*Low-risk populations are those with ARF incidence ≤2 per 100 000 school-aged children or all-age rheumatic heart disease prevalence of ≤1 per 1000 population per year.

†Subclinical carditis indicates echocardiographic valvulitis as defined in Table 3.

‡See section on polyarthralgia, which should only be considered as a major manifestation in moderate- to high-risk populations after exclusion of other causes. As in past versions of the criteria, erythema marginatum and subcutaneous nodules are rarely "stand-alone" major criteria. Additionally, joint manifestations can only be considered in either the major or minor categories but not both in the same patient.

§CRP value must be greater than upper limit of normal for laboratory. Also, because ESR may evolve during the course of ARF, peak ESR values should be used.

Treatment of ARF

Treatment of ARF includes controlling inflammation with aspirin or a nonsteroidal anti-inflammatory drug (NSAID) such as naproxen, management of acute carditis and heart failure in severe cases, GAS eradication and preventing repeated episodes of ARF by commencing patients on penicillin prophylaxis. The rapid response of arthritis to NSAIDs is one of the hallmarks of the joint pain associated with ARF. Bed rest is also recommended for patients with acute presentation [18].

Conventional anti-failure treatment is usually initiated in those presenting with heart failure. This will include diuretics and angiotensin-converting-enzyme inhibitors. Valve surgery is not recommended in the acute phase due to poor outcomes, although severe intractable heart failure in the face of ARF is an indication for emergency surgery [18].

Treatment with penicillin for the eradication of GAS infection consists of benzathine penicillin G intramuscular or penicillin VK orally for 10 days. Secondary penicillin prophylaxis should be instituted once the diagnosis of ARF is made, either as a daily oral dose or intramuscular injections monthly (see Table 2). Those with a penicillin allergy are rather given a narrow spectrum cephalosporin [18].Of note, in some countries such as South Africa, ARF is a notifiable condition [26]) .

Table 2: Primary and Secondary prevention, from Zühlke et al [18].

Primary prevention (treatment of GAS pharyngitis)

Agent	Dose	Route	Duration
Benzathine penicillin G	≥27 kg: 1.2 million units	IM injection	Once
	<27 kg: 600,000 units		
Penicillin V	Children 250 mg, × 2-3/d	Oral	10 d
	Adults 500 mg, × 2-3/d		

If penicillin allergy, options include narrow spectrum cephalosporin, clindamycin, azithromycin and clarithromycin. Consult local guidelines or see American Heart Association Guideline[81]

Secondary prevention (prevention of recurrent attacks)[a]

Agent	Dose	Route	Duration
Benzathine penicillin G	≥20 kg: 1.2 million units (<20 kg: 600,000 units) every 4 wk[b]	IM injection	
Penicillin V	250 mg × 2/d	Oral	
Erythromycin	250 mg × 2/d	Oral	

[a] Duration of secondary prophylaxisdepends on history of carditis and if valvular involvement persists. In most cases, minimum duration is 10 years since last ARF episode or until age 21 years, whichever is longer, with prolongation until age 35-40 years in individuals with significant valvular disease.

[b] Although 4-weekly injections are effective if good adherence can be assured, benzathine penicillin G may be given more frequently –every 3 or every 2 weeks –if there is a desire to further increase the efficacy in preventing recurrent ARF.

IM, intramuscular, kg-kilograms

Rheumatic Heart Disease

Global Burden of RHD

RHD is the direct sequel of ARF and can present asymptomatically or symptomatically with chronic valvular heart disease. It is associated with major complications such as heart failure, pulmonary hypertension, stroke or transient ischemic attack, infective endocarditis, atrial fibrillation, prosthetic valve thrombosis in those who underwent valve replacement, major bleeding as well as death [18].

Global age-standardized mortality due to RHD has reduced by almost 50% from 1990 to 2015 [2].Compounded with the near eradication of ARF and RHD in higher income countries, this has led to the overshadowing of the high burden of disease in lower- and middle-income countries. At the time the study was conducted, the Global Burden of Disease study estimated about 33,4 million people living with RHD and an estimated death toll of 319 400. The countries with the highest number of deaths due to RHD were India, China and Pakistan, while the highest age-standardized prevalence was found in Oceania, followed by sub-Saharan Africa and then South Asia [2]. Rheumatic heart disease, like its precursor ARF, is a disease of poverty affecting mostly the young and leading to considerable morbidity and mortality. It is a leading cause of

acquired heart disease among children in low- and middle-income countries where there is often a shortage of human resources and facilities for its diagnosis and management. It is the second most common cause of heart failure in sub-Saharan Africa following hypertension and the second most common cause of children admitted with heart failure in rural district hospitals in Rwanda [28, 29] .

If presenting in childhood, RHD can lead to complications in early adulthood, most commonly in young pregnant women. Pregnant mothers presenting with a history of known heart disease are at the highest risk for poor maternal and fetal outcomes. The confidential maternal death enquiry in South Africa of 2011-2013 showed that RHD and its complications were the second leading cause of cardiac death in the in peripartum period, following peripartum cardiomyopathy [30] .

The increase in asymptomatic RHD screening with echocardiography has shown a higher disease burden of RHD than initially estimated with clinical (auscultation-based) screening efforts. The distribution of this still resembles that of symptomatic RHD, with lower-income countries hit the hardest. A meta-analysis of contemporary echo-based studies showed a pooled global prevalence of 26% for asymptomatic RHD. In South Africa, the prevalence of asymptomatic RHD was estimated to be 20,2 cases per 1000 school-going children in an echocardiographic screening survey performed in Cape Town [3, 31] .

Characteristics of Rheumatic Valvular Heart Disease

Rheumatic heart disease is characterized by a chronic fibrotic process involving the heart pericardium (pericarditis), inflammatory tissue infiltration of the myocardium in the form of granulomas (Aschoff nodules) and can lead to a valvulitis with permanent heart valve damage. Chronic rheumatic valvular disease develops years following one or repeated episodes of ARF. A prospective follow-up of 258 Brazilian children and adolescents with ARF ranging from 2-15 years, showed that 186 of them (72%) developed chronic valve disease [32].

Pattern of Valve Lesion Involvement

The most common valve pathology is mitral valve disease followed by aortic valve disease. Mitral regurgitation (MR) remains the most common presenting lesion in those younger than 30 years, however there may be a longer asymptomatic period as a higher volume load can be tolerated for years [33].Some of the echo features include elongated chordae causing prolapse of the anterior mitral valve leaflet (AML) and chordal rupture which can present with a flailing AML. When presenting late in the disease natural history, it can already be associated with significant left ventricular dysfunction. A retrospective survey of echocardiographic patterns in children with RHD at the Uganda Heart Institute in Mulago Hospital showed that MR was the most prevalent valve lesion. Furthermore, it demonstrated that 73,1% of children with MR

presented with severe disease and 68,4% had left ventricular systolic dysfunction [34]
.
Mitral stenosis (MS) alone is more common in those older than 30 years. The terms 'dog leg' or 'hockey stick' deformities are used to describe the morphological features seen on echocardiography with MS. These include doming of the AML, as well as shortening, thickening and calcification of the leaflet. It is more associated with complications of RHD such as heart failure, atrial fibrillation, pulmonary hypertension and stroke. In pregnancy, MS as the predominant lesion can lead to fatal outcomes for both the mother and the fetus. It is the pathognomonic lesion of RHD in young adults after excluding congenital mitral stenosis [33].

Aortic valve lesion involvement is usually associated with mitral valve lesion disease. Isolated aortic regurgitation (AR) is more common in chronic rheumatic valve disease than isolated aortic stenosis (AS) and is often found as mixed aortic valve disease. On echocardiography, fusion of the commissures of the aortic valve with restriction in leaflet motion is seen with AS and a coaptation defect while leaflet prolapse is seen with AR. Tricuspid valve disease is not as common, but can present in association with existing mitral valve disease and/or aortic valve disease (left-sided valvular heart disease). Pulmonary valve disease is also not a common feature of RHD [33].

RHD is the most common cause of mixed valvular heart disease. This is a combination of stenotic and regurgitant lesions in one or more heart valves and is associated with a worse prognosis. The frequency of mixed valve disease presentation varies amongst the different paediatric RHD registries as well as the pattern on the specific valves involved. The common variable is that they present with a more complex natural history and this affects the clinical presentation as well as the management. Patients with mixed valvular disease require valve replacement when symptomatic [35].

Diagnosis of RHD

The diagnosis of RHD is usually suspected following presentation with a clinically detected heart murmur and/or signs and symptoms of heart failure (such as effort intolerance and shortness of breath) with or without a past history of RHD.

The 2012 World Heart Federation (WHF) criteria for the diagnosis of subclinical echo-confirmed RHD in asymptomatic individuals suggests doppler criteria for subclinical disease. It outlines the pathological and morphological features of valve lesions suggestive of RHD. Patients may not recall a previous diagnosis of ARF, in which case they will be classified as either borderline or definite RHD [26].However, these patients present a different cohort to clinical case detection, especially in children. The presentation of rheumatic valvular heart disease in the paediatric population in endemic areas is rapidly progressive and younger children present with severe lesions

compared to their counterparts in non-endemic areas [18].Multivalvular heart disease is more common in the older adult population [35].

The New York Heart Association (NYHA) classification is a risk-stratification tool that is used to categorize patients with heart failure by their severity in order to monitor and plan the management of heart disease. It is commonly used and applied to adults and adolescents. An adaptation of the NYHA classification is the Ross classification for young children or neonates. This system uses history of feeding intolerance, growth patterns, exercise intolerance and physical features on exam to describe the severity of heart failure [36].

Medical Management of RHD

Basic medical therapy for RHD involves management of presenting heart failure with anti-failure medications, prophylaxis against recurrent ARF with benzathine penicillin (intramuscular or oral) as well as medical management of presenting complications including thromboembolism prevention. The management of heart failure is usually aimed at reducing symptoms and improving quality of life. Pharmacological therapy in the form of diuretics, angiotensin converting enzymes, beta blockers and mineralocorticoid receptor antagonists can be initiated. Digoxin can be considered for those who are symptomatic despite mainstay anti-failure treatment [36].Prophylaxis against recurrent ARF in those with RHD needs to be instituted. Patients should ideally be registered with regional prevention programmes and the duration of prophylaxis is prescribed according to the severity of the lesion and the period since the last episode of ARF [18] .

An anticoagulant such as warfarin is recommended in patients with rheumatic mitral stenosis presenting with either atrial fibrillation, a previous embolic event or left atrial thrombosis [36]. In general, patients presenting with valvular heart disease require close clinical monitoring as well as regular echocardiograms to monitor progression and need for surgical intervention by qualified skilled professionals.

Vascular Catheter Interventions and Valve Surgery

Catheter intervention depends on the valve morphology presenting and the presence of mixed valve disease. In the case of mixed valve disease, catheter intervention is usually unsuitable as a curative measure. Percutaneous valvotomy is therefore useful for repair in patients with isolated lesions such as MS and minimizes the risk of surgery. Severe valve stenosis can be treated with interventional balloon valvuloplasty, usually for mitral and aortic valves but in rare cases also involving the tricuspid and pulmonary valves. These can be life-changing and provide a significant period of stability without the need for further intervention [33].

Severe valvular disease, including mixed valve disease, requires surgical treatment involving valve repair or valve replacement together with valvuloplasty on additional valves, for example MV replacement for mixed MV disease with a tricuspid annuloplasty. With regards to surgery, valve repair is preferred above replacement as the surgical option of choice if anatomically possible. A repair will negate the need for anticoagulant therapy required following valve replacements. This is especially important in the younger population, women of child-bearing age and resource-limited countries where provision of warfarin, international normalised ratio (INR) monitoring and proper INR control is difficult. RHD is a pro-thrombotic condition which poses a significant risk of bleeding and stroke due to poor INR control, specifically to pregnant women, the unborn fetus, and to both during the subsequent post-natal period [33].

Indications for surgery largely depend on the type or pattern of valve lesion involvement. With regards to MR, left ventricular (LV) systolic dysfunction with a left ventricular ejection fraction (LVEF) <60% and/or an end systolic ventricular dimension of >4cm, are indications for valve surgery [37].Mitral valve repair has a 5-year greater survival than replacement, but in many cases, especially if surgery is performed in childhood, patients are more likely to require re-operation due to ongoing fibrosis [38]. Surgical indications for AR include severe symptomatic AR with LV function decreasing and increased LV size. Valve replacement is the surgical option of choice for severe AS, which is symptomatic, but for mixed AV lesions valve replacement is preferable. For tricuspid valve stenosis (TS), balloon valvuloplasty can be an option, but not if accompanied by left-sided valve disease. In this case full valve repair will be required [37].

Access to Surgery for RHD Populations

Valvuloplasty and valve surgery services are mostly only accessible to those in higher income countries. According to an international multi-centre RHD registry, 61% of adults and children who underwent valve surgery did so in upper-middle-income countries compared to 25% in lower-middle-income countries and 11% in low-income countries. This is mainly due to the lack of facilities and expert resources [6].

The vast majority of people living with RHD reside in countries without comprehensive surgical programmes or only have programmes run independently in-country. Thus RHD-interventions are at a premium and only a few are able to access these surgical and catheter-based interventions. In sub-Saharan Africa, excluding South Africa, there are only about 22 cardiac centres to service a population group that would otherwise require about 400 centres [18] .The Cape Town Declaration on access to cardiac surgery in the developing world proposed the establishment of working groups of experts from the field, industry and government representatives to develop

specialised cardiac care in these areas. It also called for the training of cardiac surgeons and specialised caregivers in low- to middle-income countries [39].

RHD Global Policy

Although RHD has been largely ignored by the global North and public health agencies, the Sustainable Development Goals (SDGs) strategy adopted by the United Nations General Assembly on 25 September 2015 in New York encouraged global health agencies such as the WHO and WHF to review their stance on RHD, resulting in a renewed focus and reinvigorated research efforts over the last decade [40].The WHF published a declaration for the eradication of 25% of premature deaths due to cardiovascular heart disease in individuals younger than 25 years by 2025 [41] .Multiple medical research groups have also published public declarations focusing on RHD, led by the Pan-African Society of Cardiology (PASCAR) [42].

The Addis Ababa communiqué, a joint coalition between the African Union Commission together with PASCAR and experts in the field, highlights the seven key actions to eradicate RHD in Africa which were discussed during the Third All-Africa Workshop on ARF and RHD held in February 2015 [5] .Two particular actions include creating prospective disease registries in affected areas and ensuring adequate supply of high-quality benzathine penicillin for the primary and the secondary prevention of ARF. There is a current public health crisis as penicillin, despite being a WHO essential drug, experiences frequent stock-outs in many areas of the world and is only manufactured in two or three factories. Other actions also include improving access to reproductive health care services for women with RHD, decentralising technical expertise involved in the diagnosis and management of ARF and RHD as well as creating centres of excellence for essential cardiac surgery. They also emphasised the importance of creating national multisector RHD programmes within NCD control programmes and strengthening international partnerships with multinational organisations for resource mobilisation [5].

The 71st World Health Assembly Resolution on RHD, passed in May 2018, provides the global plan for combating this preventable disease [9]. It addresses the global shortage of medicines like penicillin and vaccines, their safety and efficacy, as well as efforts to end poverty which is a major risk factor for ARF. The Resolution urges member states to address the socio-economic conditions of their countries, estimate burden of disease in endemic areas, ensure access to health care and strengthen efforts pertaining to international cooperation for eradicating RHD [9].The fight to eradicate RHD is in essence the fight to end poverty and ensure access to quality health care.

RHD is largely a disease of children and young people and is the major cause of acquired heart disease within this group. As this is also a disease of pregnant women,

families losing mothers are also indirect victims. Efforts to eradicate RHD will therefore lead to better quality of life for both children and their families.

The Need for RHD Registries

One of the key actions mentioned in both the Awareness, Surveillance, Advocacy and Prevention (A.S.A.P.) programme and Addis Ababa communiqué was the need for more contemporary research on ARF/RHD in endemic countries and diverse populations [5, 43]. Improved data collection and robust disease estimates are needed in low- to middle-income countries to accurately depict the burden in these areas. Of note is the need to determine the fatal and non-fatal outcomes of patients to guide the control of RHD.

Several registries such as the VALVAFRIC registry, the Uganda Heart Institute Registry and the first multi-centre prospective registry for RHD in low- and middle-income countries, called the REMEDY Study, have been established in Africa [6, 8, 34]. The Global Rheumatic Heart Disease Registry (REMEDY Study), includes data on 3 343 hospital-based patients from 12 countries in Africa, Yemen and India with symptomatic RHD. Findings from the REMEDY Study showed that most patients were young, female and unemployed, presenting with predominantly moderate to severe heart disease. There was also unequal access to interventions like surgery between low-income, lower-middle-income and upper-middle-income countries. Several factors were found to be associated with a higher risk of mortality in the entire population group namely, the severity of valve lesions, congestive heart failure, NYHA functional classification III/IV, atrial fibrillation and increasing age. Level of education in terms of years post primary education as well as female gender were found to be protective [6].

RHD in Paediatrics

For decades, the paediatric population has largely been ignored in the global NCD agenda. Although ARF is a childhood disease, RHD is predominantly a disease of young adults and adolescents. Similarly, ARF/RHD fits between the silos of infectious diseases (GAS), auto-immune diseases (ARF) and non-communicable diseases (RHD) with the socio-economic public health component being crucial to management and prevention. This has resulted in a lack of consensus activity and subsequent funding for research and development, particularly in children presenting with and, affected by, severe RHD.

Amongst the studies focused on children with RHD, the Uganda Heart Institute set out to describe the echo pattern and severity of valve dysfunction in children with RHD from its registry, retrospectively from January 2007 to December 2011. They enrolled 376 children with RHD (mean age: 11 years, mainly female) with MV regurgitation as the most common valve lesion involvement, AR more common in males and MS as the

least prevalent lesion. The study showed that most of their childhood population presented with severe disease (73,1%) [34].

In India, at the All India Institute of Medical Sciences in New Delhi, the 385 children enrolled in their registry had a female predominance with a greater burden of effort intolerance than their male counterparts at presentation, and a NYHA classification of III to IV in 26% of the female children compared to the 13,8% in the males. They found that 71.9% of the children presented with severe valvular disease, again more so the females than the males. The study had 248 patients requiring valve lesion surgical interventions; only 53 of them had undergone such interventions within an 11-month follow-up period. Characteristics of those needing interventions were NYHA class III-IV, MS presentation and mixed mitral valve disease. Adherence to penicillin was high (93%) and 14 patients died within the follow-up period (3,1%) [7].

Summary and Conclusions

RHD is a significant cause of acquired and preventable cardiovascular disease with severe complications. Recent literature has revealed unequal access to care in low- and middle-income countries for those living with RHD. The use of patient registries to quantify the burden of the problem and evaluate the nature and outcomes of the disease has contributed to the contemporary knowledge on RHD.

Only single-centre studies focusing on children have been done to date, showing that children with RHD presenting to tertiary institutions are severely affected and have different characteristics in terms of presentation than those seen in adults. In this study, we will examine the presentation, clinical characteristics and specific evidence-based interventions and outcomes of the disease among the pediatric population of patients enrolled in the REMEDY registry. We aim to identify the risk factors associated with mortality in the patients below 19 years of age, discuss the specific evidence-based interventions and suggest possible interventions to reduce morbidity and mortality in this population.

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Chapter 2: Publication-Ready Manuscript

Clinical characteristics and outcomes of children with Rheumatic Heart Disease: A Global Rheumatic Heart Disease Registry (REMEDY) sub-analysis

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Abstract:

Background:

Despite Rheumatic Heart Disease (RHD) contributing to an estimated disease burden in 2019 of 40 million people and 285 500 deaths, few studies document the characteristics and outcomes in children. We undertook a sub-analysis of children from the multi-centre prospective two-year global Rheumatic Heart Disease Registry (REMEDY) to document their presentation, clinical characteristics and outcomes.

Methods:

Nine-hundred and twenty-one children were enrolled into the REMEDY registry among the 3,343 symptomatic RHD patients from 25 hospitals in 12 African countries, India and Yemen and followed up over 24 months to assess characteristics, complications and outcome.

Results:

More than half of the children enrolled in the REMEDY study presented with severe valvular heart disease; 60% had more than one valve involved, 30% were classified as NYHA class III/IV and 17.7% died within 24 months. Just over 20% of children were not on penicillin prophylaxis. Although 20% met criteria for surgery, only less than 9% (n=78, 8.5%) had had percutaneous or surgical intervention with half from upper-middle-income countries. The major risk factors associated with mortality included older age (Hazard Ratio (HR): 1.01, p=0.001) and atrial fibrillation or flutter (HR: 2.3, p=0.028). Female gender (HR: 0.68, p=0.062) and education level above primary school (HR: 0.88, p=0.68) did not confer significant protection. However, a past medical history of ARF conferred some protection against mortality (HR: 0.61, p=0.031). In follow-up, 30% (n=238, 29.6%) of children experienced an adverse cardiovascular event, nearly 15% (n=114, 14.1%) were hospitalised and six young women became pregnant during the study period.

Conclusion:

Children with RHD in low- and middle-income countries are severely affected, with significant mortality and morbidity. The use of penicillin was suboptimal and the substantial need for surgery is evident. Our findings support the recommendations of the World Health Assembly (WHA) Resolution 71.14 passed in May 2018 for consistent provision of penicillin, integrated collaborative efforts focused on children and adolescent health as well as access to specialised services including cardiac surgery.

Key words: Rheumatic Heart Disease, Registries, Children

Background

Rheumatic Heart Disease (RHD) and its antecedent Acute Rheumatic Fever (ARF) are the topmost causes of acquired heart disease in children, adolescents and young adults.[44] They disproportionately affect those living in poverty and areas of inequality, and cause significant morbidity and mortality in vulnerable populations such as pregnant women.

It is essential that ARF and its sequel, RHD remain in the forefront of the global health agenda to reduce mortality and morbidity from this preventable condition, especially when the Global Burden of Disease study has highlighted the continued plight of those in low- and middle-income countries (LMICs). The world has seen a global reduction in the age-standardized mortality due to RHD by 47,8% (95% confidence interval 44,7% to 50,9%) from 1990 to 2015 yet, there is still a very high burden of disease in regions such as South Asia, Sub-Saharan Africa and Oceania [45]. To address this burden, one of the key actions mentioned in both the Drakensberg Declaration's Awareness, Surveillance, Advocacy and Prevention (A.S.A.P.) programme and the Addis Ababa communiqué, a joint coalition between the African Union Commission together with PASCAR and the experts in the field, was the need for more contemporary research in ARF/RHD in endemic countries and diverse populations [46]. Emphasis was placed on improved data collection and robust disease estimates in LMICs to accurately depict the burden. Of note is the need to determine the fatal and non-fatal outcomes of RHD patients.

RHD registries have recently been established in Africa, examples being the VALVAFRIC registry [47], the Ugandan Heart Institute registry[48] and the first multi-center prospective registry for RHD in LMICs, The Global Rheumatic Heart Disease Registry (the REMEDY Study) [49]. REMEDY included data of 3343 hospital-based patients with symptomatic RHD from 12 countries in Africa, Yemen and India. Previous reports on the rationale, baseline characteristics and two-year follow-up outcomes of REMEDY have detailed important findings, including that the patients were predominantly young, female and unemployed presenting with predominantly moderate to severe heart disease [50-52] .Concerning treatment options, there was unequal access to interventions like surgery between low-, lower-middle- and upper-middle-income countries. REMEDY further identified seven risk factors associated with a higher risk of mortality in the entire population group which included severity of valve lesions, congestive heart failure, New York Heart Association (NYHA) functional classification III/IV, atrial fibrillation and increasing age. Factors including level of education in terms of years post-primary education, as well as the female gender were found to be protective [51].

For decades, the paediatric population has largely been ignored in the global non-communicable disease (NCD) agenda, given the focus on childhood mortality from preventable deaths. Although ARF is a childhood disease, RHD is predominantly a disease of adolescents and young adults. ARF/RHD fits between the "silos" of infectious disease (pharyngitis or skin infection (Strep A)), autoimmune disease (ARF) and non-communicable disease (RHD) with the socio-economic public health component being crucial to management and prevention. This has resulted in a lack of consensus activity and funding for research and development, particularly in children presenting with, and affected by, severe RHD.

Amongst the studies focused on children with RHD, the Ugandan Heart Institute set out to describe the echo pattern and severity of valve dysfunction in children with RHD in a retrospective registry from January 2007 to December 2011 [53] .Three-hundred and seventy-six children with RHD (mean age: 11 years, majority female) were enrolled. Mitral valve regurgitation was the most common valve lesion, aortic regurgitation was more abundant in males, while mitral stenosis was the least prevalent lesion. The study showed that most of their childhood population presented with severe disease (73,1%). In another study, the All India Institute of Medical Sciences (AIIMS) in New Delhi enrolled 385 children in their registry and found that these had a greater female predominance, with a greater burden of effort intolerance than their male counterparts at presentation.[54] They documented a NYHA classification of III to IV in 26% of the female children compared with the 13,8% in the males. Seventy-two percent of the children presented with severe valvular disease, again with preponderance in females. The study indicated that 248 patients required valve lesion surgical interventions for NYHA classification III-IV, mitral stenosis presentation and mixed mitral valve disease. However, only 53 had undergone such interventions within an 11-month follow-up period. Adherence to penicillin was high at 93% 14 (3,1%) patients died within the follow-up period.

Given that mostly only single-centre studies have been conducted to date, we sought to document the presentation, clinical characteristics, evidence-based interventions and outcomes of RHD amongst the pediatric population of patients in the REMEDY registry. We identify the risk factors associated with mortality in these patients aged below 19 years, discuss the specific evidence-based interventions for this community and highlight possible interventions to reduce morbidity and mortality.

Methods

Study Population: Recruitment and Enrolment

Between January 2010 and November 2012, hospital-based patients from 12 countries in Africa (Botswana, Egypt, Ethiopia, Mozambique, Nigeria, Rwanda, Sudan,

Uganda, Kenya, Namibia, South Africa and Zambia) Yemen and India with a primary diagnosis of RHD based on clinical and echocardiographic criteria were enrolled in a population-based clinical registry, REMEDY, with the aim of understanding the characteristics, complications, gaps in evidence-based interventions and outcomes of the disease.[50]

Inclusion Criteria

Children were defined as those patients less than 19 years of age at the time of enrolment who had a diagnosis of RHD and were seen at outpatient facilities, emergency departments, or inpatient facilities of the participating hospitals. Patients were not deemed eligible if the primary diagnosis of valvular disease was other than RHD (e.g. degenerative disease) or if there was no informed consent/assent.

Recruitment

Demographic data, clinical findings, and details of electrocardiographic (ECG) and echocardiographic (echo) findings were recorded on case report forms at research sites and transmitted to the University of Cape Town Department of Medicine Project Coordinating Office. These were captured on a database hosted by the Population Health Research Institute at Hamilton Health Sciences and McMaster University, Hamilton, Ontario, Canada. Patients were followed up over two years and information pertaining to outcomes and death were captured from medical records and patient interviews in accordance with the REMEDY protocol. (See Follow-up and Outcome CRFs in Appendix).

Sample Size and Statistical Analysis

Data from 921 children were retrieved from the 3343 participants enrolled into REMEDY. This study was, therefore, not powered for individual outcomes in children. Prevalence estimates are presented as percentages, and as per 1,000 population with 95% confidence intervals. Continuous variables are expressed as means with standard deviations, or medians with interquartile ranges, as appropriate. Categorical variables are expressed as frequencies and percentages. Linear regression models assessed the relationship between the variables. The cumulative probability of surviving death over the follow up period comparing the different risk factors is presented as hazard ratios and the Log rank test is used to assess its statistical significance. This was expressed as a p value and 1% used to denote statistical significance. Kaplan-Meier graphs were used to display outcomes between the populations of interest over time. Cox regression models were used to assess the risk of mortality, using significant baseline variables. All analyses were performed using Stata version 16 (StataCorp LP)

Informed Consent Process and Ethics

Ethics approval was granted for the REMEDY study (HREC 026/2008). All patients provided informed consent or assent, as appropriate, to be enrolled in the study. This sub-study (HREC 220/2019) only utilised data collected during the REMEDY study. The study conformed to the principles outlined in the Helsinki Declaration (2008).

Results

Baseline Characteristics

This sub-analysis comprises 921 children aged <19 years, gender breakdown was 416 (45,2%) male and 505 (54,8 %) female. By age stratum, 24 were below 6 years (2.6%), 161 (17.5%) aged 6 to 10 years and 736 (79.9%) between 11 and 18 years of age. 405 (44.0%) enrolled from low-income countries , 349 (37.9%)were from lower-middle-income countries and 167 (18.1%) were from upper-middle-income countries . Most children were of normal weight; amongst girls, 472 (93.8%) were normal, 23 (4.6%) could be classified as thin and 8 (1.6%) as overweight. Among boys 321 (76.8%) were of normal weight, 72 (17.2%) underweight, 13 (3.1%) overweight and 12 (2.9%) were obese.

Past Medical History at Baseline

In total, 206 (22.4%) children had signs of congestive cardiac failure at presentation (see Table 1). This was more pronounced in younger children (<6 years) versus those in the older groups (11-17 years), p=0.003. By contrast, there were only two children in the 6 – 10 year age category with atrial fibrillation or flutter compared with 29 in the older age category (11 – 17 years), p<0.0001. Seven children (0.8%) had had a percutaneous valvuloplasty while 71 (7.8%) of the remaining 914 had had previous valve surgery.

Table 1: Past medical history and presenting complaints

	Up to 6 years n=24 (%)	6 to 10 years n=161* (%)	11 to 18 years n=736* (%)	P value	Children n=921* (%)	Adults n=2418* (%)	P value
Atrial Fibrillation/Flutter	0	2/132(1.5)	29/549 (5.2)	0.1	31/698 (4.4)	553/1923 (28.8)	<0.01
Clinical Congestive Cardiac Failure at enrolment	10 (41.7)	52 (32.3)	144 (19.6)	<0.01	206 (22.4)	253 (10.5)	<0.01
Clinical Pulmonary Hypertension	6 (25)	50 (31)	192/730 (26.3)	0.6	248(27)	569 (23.7)	<0.01
Complications	0	11 (6.8)	65/733 (8.8)	0.2	76 (8.3)	348 (14.5)	<0.01
Infective Endocarditis	0	6 (3.7)	42/732 (5.7)	0.3	48/917 (5.2)	85/2400 (3.5)	0.03
NYHA III/IV	10 (41.7)	64 (39.8)	209/718 (29.1)	0.02	283/913 (31.3)	526/2380 (22.1)	<0.01
Major Bleeding	0	5 (3.1)	16/733 (2.2)	0.6	21/918 (2.3)	68/2398 (2.84)	0.38
Peripheral Embolism	0	0	2/918 (0.3)	0.8	2/918 (0.2)	23/2389 (0.96)	0.03
Previous Congestive Cardiac Failure	16 (66.7)	93 (57.8)	295/731 (40.4)	<0.01	404/916 (44.1)	705/2403 (29.3)	<0.01
Rheumatic Fever in the past	12 (50)	86 (54.4)	322/725 (44.4)	0.3	420/907 (46.3)	919/2384 (38.6)	<0.01
Stroke/Transient Ischaemic Attacks	0	3	17	0.7	20/918 (2.18)	215/2404 (8.9)	<0.01
Percutaneous Valvuloplasty	0	1 (0.6)	6/733 (0.8)	0.8	7/134 (4.04)	127/2400 (5.3)	<0.01
Previous heart valve surgery	0	7 (4.3)	64/671 (9.5)	0.06	71/920 (7.7)	641/2409 (26.6)	<0.01

* Available Data

Valve involvement

Of 883 children, 351 (39.8%) had only one valve involved, 358 (40.5%) two, 130 (14.7%) three and 44 (5.0%) children had all four valves involved in the RHD process. (Table 2)

Table 2: Numbers of valves involved in Children and Adults

	Number of valves involved				
	1	2	3	4	Total
Age category					
<6, n (%)	16 (66.7)	5 (20.8)	2 (8.3)	1 (4.2)	24
6-11 years, n (%)	73 (46.2)	60 (38.0)	17 (10.8)	8 (5.1)	158*
12-18 years, n (%)	262 (37.2)	293 (41.8)	111 (15.8)	35 (5.0)	701*
Children Total, n (%)	351 (39.8)	358 (40.5)	130 (14.7)	44 (5.0)	883*
Adults, n (%)	746 (33.3)	998 (44.6)	459 (20.5)	35 (1.6)	2238*
Grand Total, n (%)	1097 (35.1)	1356 (43.4)	589 (18.9)	79 (2.5)	3121*

* Available Data

The pattern of valve involvement in native valves across the three age categories is depicted in Figure 1. In the under 6 age category, pure MR remains the most common valve pathology (63%), but with significant numbers of mixed mitral valve disease (8%) and mixed aortic and mitral valve disease (4%) mitral and aortic regurgitation. In the older age category in children (11-18 years), the figure shows increasing percentage of pure MS (3%), decreasing percentages of pure MR (35%) but now with mixed mitral valve disease, mixed mitral and mixed aortic valve disease (which also includes a small number of tricuspid and pulmonary stenoses) and a small number (2%) of isolated aortic valve disease (either pure aortic regurgitation or pure aortic stenosis).

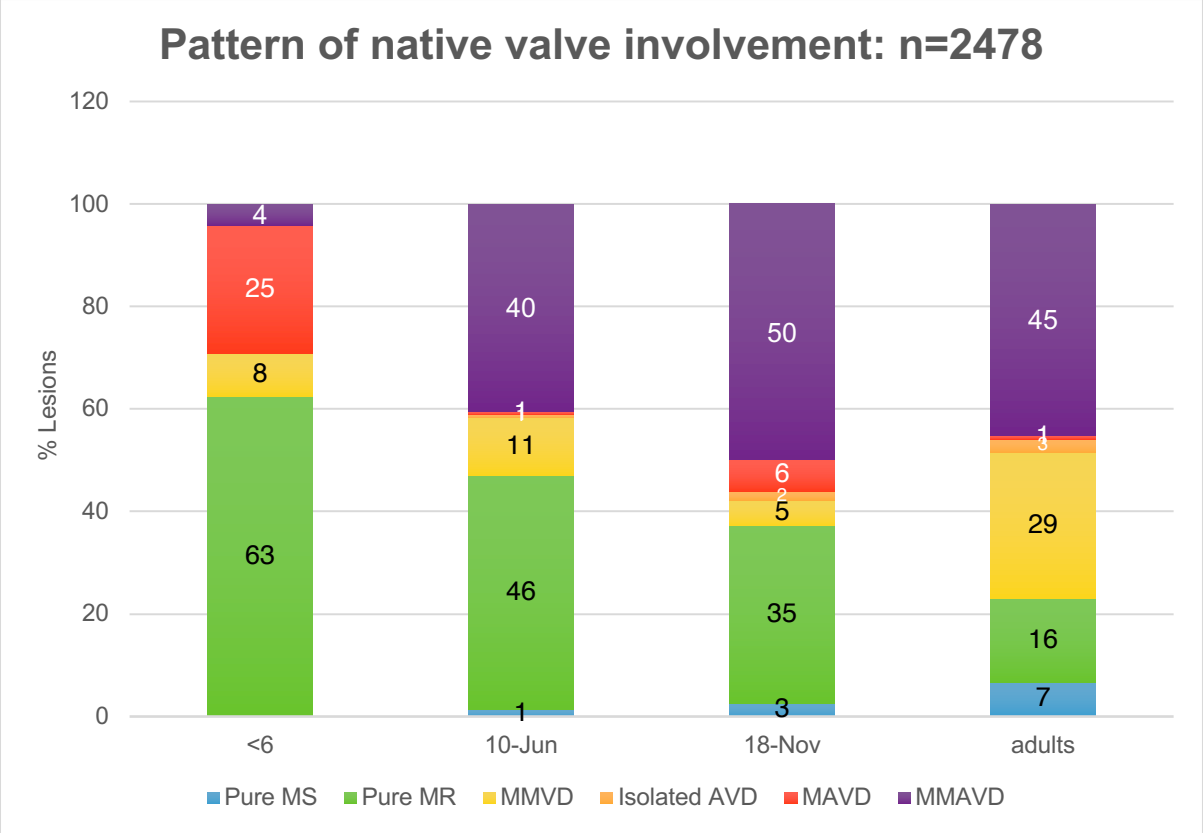

Figure 1: Pattern of valve involvement

Echo Findings at Baseline

Almost twenty percent (168/880, 19.1% *available data) of children had a decreased ejection fraction at enrolment, while more than half (50.8%) of all children with available echo data, had a dilated left ventricle. The mean left atrial diameter in children was 49.3mm (SD: 12.5).

Penicillin

Only 78.6% (704/896, *available data) of children were on penicillin prophylaxis, the vast majority (n=635/704, 90.1%) of whom were on benzathine penicillin.

Indications for Surgery

More than half (n=469, 55.5%) of all children enrolled were designated as having severe valve disease. A third (n=282, 31.3%) were in NYHA categories III and IV. There were 69 (47.3%) children in the category of severe MR with mild to moderate LV dysfunction, and 170 (40%) children in the category of severe MR with a dilated LV. In those with native valves, almost two-thirds (n=570/816, 61.8%) have more than one valve involved.

Outcomes

Loss to Follow-up

In this study, 120 (13.0%) of the total paediatric cohort, were lost to follow-up with no visits after enrolment.

Events

Mortality

142 of the 801 paediatric participants with follow-up data (17.7%) died. There was a significant difference between the girls and boys with lower mortality in girls (63/442, 14.3%) compared to boys (79/337, 23.4%), p=0.0027) on univariate analysis; however, this did not remain significant in a multivariate model.

Risk Profiles

In children, the major risk factors associated with mortality included increased age (Hazard Ratio (HR): 1.01, p=0.001), atrial fibrillation or flutter (HR: 2.3, p=0.028), NYHA III & IV (HR: 2.4, p<0.001), and severe valve disease (HR: 4.7, p<0.001). However, female sex (HR: 0.68, p=0.062) and education level above primary school (HR: 0.88, p=0.68) did not confer significant protection. Significant protection was conferred by a previous history of ARF (HR: 0.61, p=0.031), in those with a past history of ARF, 10.2% died compared to 19.6% who had no documented ARF (Log rank Chi = 16.41, p> 0.001) (see Figure 2). Those who had undergone surgery or valvuloplasty had a 10,3% mortality compared to those with native valves (15.8%); this was, however, not statistically significant (p=0.19).

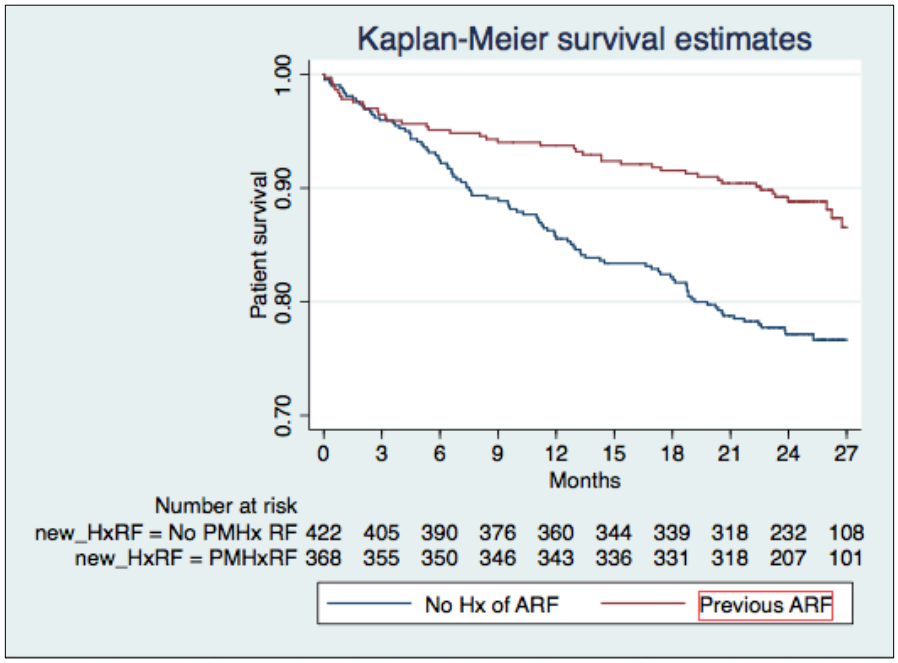

Figure 2 : Survival according to having a previously documented episode of Acute Rheumatic Fever

Table 3 depicts the adverse cardiovascular events, pregnancies and surgeries during the 24-month period. Almost 30% (n=244, 29.6%) of children experienced an adverse cardiovascular event during the period, almost 15% (n=114, 14.1%) were hospitalised during the period and six became pregnant. A total of 63 interventions (55 surgeries and eight percutaneous procedures) were performed; of which 2.7% were in low-income, 4.6% in low-middle-income and 16.7% in upper-middle-income groups (p=0.01).

Table 3: Adverse cardiovascular events, pregnancies and surgeries in children

		Total n	Incidence proportion
Cardiovascular Events	Hospitalisation	114	14.2
	Congestive Cardiac Failure	69	8.5
	Atrial Fibrilation	16	2.0
	Acute Rheumatic Fever Recurrence	11	0.6
	Infective Endocarditis	10	1.2
	Pregnancy	6	0.7
	Prosthetic Valve Thrombosis	5	1.0
	Major Bleeding	5	1.0
	Stroke	4	0.5
	Pulmonary Embolism	3	0.4
	Systemic Embolism	1	0.2
Total *		244	29.9
Surgery	Valve replacement or repair	55	6.8
Percutaneous valvuloplasty		8	1.0
Deaths		142	17.7

* excludes pregnancy

Discussion

The key findings of this study were, firstly, that children were severely affected. More than half of all children in our study presented with severe valvular heart disease and almost two-thirds had more than one valve involved. Secondly, although MR was the most prevalent valve lesion in all age groups, mixed mitral and aortic valve disease and, mixed mitral valve disease became more prevalent in older children. Thirdly, a substantial percentage of children met indications for cardiac surgery: 24% with a NYHA classification of III or IV and no left ventricular dysfunction, 48% were asymptomatic with severe MR but had mild to moderate left ventricular dysfunction and 40% of asymptomatic children with severe MR also had a dilated left ventricle. Less than one-tenth (7,8%) of children were able to access valve surgery. Finally, mortality was high (15.4%) with the biggest risk factor being severity of valve disease and morbidity was sizeable with almost 40% of children developing an adverse event during the follow-up period.

The finding of the majority of children being severely affected is similar to that of two country-level registries, one from Uganda and the other from India.[53, 54] Children and adolescents in these cohorts were, however, from low-, middle- as well as upper-middle-income countries, with similar findings across the three income categories and age strata. It is clear, therefore, that RHD, although predominantly an adult disease, affects children and adolescents with advanced disease early in life. Presenting complaints and adverse clinical features were more advanced than adults in the study. This suggests that ARF may have been missed in early childhood, and that preventative strategies and integrated management of sore throat, were suboptimal in the countries enrolled in this study.

The concern of investigators that a subset of children present with accelerated disease is also noted and deserves further investigation, including histological, proteomic and genetic efforts.[55] The main REMEDY study showed a female predominance which is a frequent feature of RHD.[51] In adults, the association of female sex with adverse outcomes in RHD appears to be partially related to peri-partum risk.[56, 57] In contrast, in this study, male sex was associated with increased mortality, which could be due to poorer access to health care in boys, the working boy and no retainment/re-introduction to the healthcare through antenatal or reproductive healthcare. However, this aspect is complex and requires more investigation. We failed to demonstrate an association with severity and undernutrition although it was interesting that our children included a proportion of underweight female children, a particular at-risk group.

Most prevalent valve lesion in age groups

Although MR was the most prevalent valve lesion in all age groups, mixed mitral and aortic valve disease (50%) and mixed mitral valve disease (40%) became more prevalent in older children with pure MR being more common in the youngest age group. Presentation in children is clearly different to presentation in adults in whom MS is pathognomonic of RHD, and can be treated with balloon valvuloplasty, if indicated.[58] However, in children, pure MS is rarely seen until the second decade (although reported in younger age groups in Ethiopia and India).[59, 60] These findings highlight the need for medical management for MR, percutaneous balloon valvuloplasty for MS or ultimately valve surgery, preferably valve repair over replacement, for mixed valve disease. [61]

In addition, our study reflects the need for ongoing medical investigations to document the evolution of valve lesions and the consideration of more complex interventions in the future. Both the WHA Resolution 71.14 and the Addis Ababa communiqué stress the requirement of registries and observational studies, as well as decentralised expertise in diagnostics such as echocardiography. There have been significant inroads into decentralised and point-of-care echocardiography which can be used in remote settings to diagnose valve lesions [62, 63] and these should be incorporated into routine care.

Echocardiographic Indications for Cardiac Surgery

Published indications for cardiac surgery for valvular heart disease include echocardiographic dimensions as well as symptoms.[64, 65] In our cohort, 30% were categorised as having severe disease, and 59% had more than one affected valve. Almost 20% of children had a decreased ejection fraction and 50% had a dilated left ventricle, all indications for valve surgery. Furthermore, almost a quarter had a NYHA classification of III and IV while almost half had severe MR with mild to moderate left ventricular dysfunction. Finally, 40% of the children with severe MR also had a dilated left ventricle. Thus at least 20% of our cohort met indications for cardiac surgery at enrolment. Despite this, only 71 children (7,8%) were able to access valve surgery, with only three high-volume centres of surgery (South Africa, India and Egypt) amongst the centres included in the study affirming previous findings of there being very few high-volume centres in African countries, particularly south of the Sahara.[66] It is thus recommended that growing centres such as those in Namibia and Uganda, not only consider the specific needs of children who require surgery, but also allow for reproductive intent and longevity.[67, 68]

High Mortality Rate, Significant Morbidity

The independent predictors identified for death in our cohort, i.e. increased age, atrial fibrillation and flutter and severe valvular heart disease are similar to the findings for the entire cohort, adult and paediatric, where the independent predictors were severe valve disease, congestive heart failure, New York Heart Association functional class III/IV, atrial

fibrillation and older age at enrolment. In addition, 40% of children experienced an adverse cardiovascular event. Outside of the inherent morbidity and implications on quality of life, this also has significant implications for social functioning, schooling, family cohesion and internal family finances.

An important finding was the low rate of adherence to penicillin prophylaxis (78.6%) with the majority being on benzathine penicillin (91.1%). This is significantly higher than the 45.6% of adults on prophylaxis ($p<0.001$). Although the increased value is encouraging and should be commended especially in low-income countries, the guidelines for moderate or severe disease recommend prophylaxis for all patients, particularly so in children at continued risk for ongoing GAS infections and progression (worsening) of valve lesions. The role of penicillin in the face of severe disease, has recently come under scrutiny following some adverse events.[69] Although penicillin prophylaxis was not associated with protection against mortality, penicillin prophylaxis was most likely subsequent to a diagnosis of ARF, which was associated with protection against mortality. Shortly after the study closed, however, global shortages of penicillin ensued, which indicates that penicillin supply chains are vulnerable and need to be protected and strengthened.

Limitations of the Study

A hospital-based registry has significant inherent limitations; more symptomatic children are enrolled, while the morbidity and mortality associated with community RHD is not explored. In addition, 13% of our paediatric cohort were lost to follow-up; thus, the incidence of mortality and morbidity could therefore have been under-estimated if participants were lost due to early mortality and adverse events. Finally, similar to the parent REMEDY study, past events were reported by parents and physicians and not verified independently by the investigators.

Strengths of the Study

Use of an extensive database of previously collected clinical and demographic information allowed us to have a large enough cohort of children from different countries and income groups. As far as we are aware, this is the largest multi-centre sub-analysis of children with RHD. In addition, these findings have informed policy and practice regarding the use of penicillin, an essential medicine in the management of RHD, [70] and the need for reproductive health care.[71]

Implications for Practice, Policy and Research

We have demonstrated the need for cardiac surgical and catheter interventions in children, and consequently the importance of developing expertise in the field of paediatric cardiology and cardiothoracic surgery. This reflects the conclusions of several recent publications

highlighting the gap within cardiac surgery.[72-74] The importance of early diagnosis of ARF and early referrals of mild disease are also apparent from our findings. Finally, the need of continued access to benzathine penicillin for children diagnosed with ARF or RHD is emphasized.

Since the 2018 WHA Resolution (71.14), governments from RHD-endemic countries have been encouraged to improve control and management of RHD. However, in the face of other competing diseases and underlying fragile health systems and economies, this needs improved governance and most likely funding. Integrating RHD into current programs focused on children, such as the IMCI or WHO HEART/Pen Plus may be the best approach with limited resources. The findings of such severe disease in children and adolescents upon enrolment into our registry warrants continued efforts to develop a vaccine for this preventable disease.

Conclusion

More than half of the children enrolled in the REMEDY study presented with severe valvular heart disease and almost two-thirds had more than one valve involved. Mortality due to symptomatic RHD was 15.4% in children and associated with the severity of RHD. A past medical history of ARF conferred some protection against mortality, however, over 20% of children were not on penicillin prophylaxis. Therefore, measures must be put in place for early diagnosis of ARF and detection of asymptomatic RHD with initiation of secondary prophylaxis. We support the recommendations of the WHA Resolution 71.14 for consistent provision of penicillin, integrated collaborative efforts focused on children and adolescent health as well as access to specialised services including cardiac surgery.

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73. Zilla, P., et al., *Global Unmet Needs in Cardiac Surgery.* Glob Heart, 2018. **13**(4): p. 293-303.
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Appendices:

1. HREC Approval

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6626
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

10 April 2019

HREC REF: 220/2019

A/Prof L Zuhlke
Paediatrics Cardiology
2.17, 2nd floor
ICH Building
Red Cross War Memorial Children's Hospital

Dear A/Prof Zuhlke

PROJECT TITLE: CLINICAL CHARACTERISTICS AND OUTCOMES OF CHILDREN WITH RHEUMATIC HEART DISEASE: A GLOBAL RHEUMATIC HEART DISEASE REGISTRY (REMEDY) (SUB-STUDY LINKED TO 026/2008) (MMED CANDIDATE: DR S MAKETE)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until 30 April 2020.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

The HREC acknowledge that the student, Dr Sindiswa Makete will also be involved in this study.

Yours sincerely

pp UBurgess
PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

HREC 220/2019

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
NHREC-registration number: REC-210208-007

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

HREC 220/2019

2. Baseline CRF

Baseline Questionnaire - Demographics **Page 1**

DataFax #164 Plate #010 Visit #002

Subject ID

Centre# Subject #

Subject Initials F M L

Today's date: year month day

Enrolment visit

1. Date of birth: year month day **OR** **Age** (years) ☐ accurate ☐ estimate

2. Sex: ☐ Male

☐ Female → Is this participant pregnant? ☐ No ☐ Yes

3. Ethnicity: ☐☐ (Please refer to facing page for codes)

4. Marital status: (check one only)

☐ Never married ☐ Currently married ☐ Common law/Living with partner

☐ Widowed ☐ Separated

5. What level of formal education have you completed? (check highest level only):
(If younger than 7 years of age, check the level of formal education completed by the mother)

☐ None ☐ Secondary/High school/Higher secondary ☐ College/University

☐ Primary ☐ Trade school/Vocational school ☐ Unknown

6. Are you currently employed?

☐ No

☐ Yes → **If yes, what is your average income per month in local currency?** ☐☐☐☐☐☐☐☐

What is the local currency? _____ → **US$** ☐☐☐ (for coordinating office only)

7. (a) During your working life, what was your main occupation? _____

(b) Please indicate which group best describes your main occupation. Current or past daily activity

☐ Group 1 ☐ Group 2 ☐ Group 3 ☐ Group 4 ☐ Group 5 ☐ Group 6

☐ Group 7 ☐ Group 8 ☐ Group 9 ☐ Group 10 ☐ Group 11 ☐ Group 12

☐ Never worked ☐ Other: _____

8. Measurements:

a) Blood Pressure Systolic ☐☐☐ / Diastolic ☐☐☐ mmHg

b) Pulse rate ☐☐☐ beats/min

c) Weight ☐☐☐.☐ kg

d) Irregular rhythm ☐ No ☐ Yes

e) Height ☐☐☐.☐ cm

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DataFax #164 Plate #011 Visit #002

Subject ID

Centre# Subject #

Subject Initials F M L

9. Presenting features: Status at the enrollment visit

a) Symptoms: (please mark (X) as appropriate)

☐ Asymptomatic	☐ Chest pain	☐ Routine clinic visit
☐ Dyspnea	☐ Fever	☐ Palpitations
☐ Syncope	☐ Fatigue	☐ Other, Specify: _____

b) NYHA class → (please refer to facing page for codes)

☐ I ☐ II ☐ III ☐ IV

10. Past medical history: (As taken from doctor's notes and patient's recollection)

		Date		Source documents available	Additional Relevant Details:
a) Congestive heart failure/ Pulmonary edema	☐ No ☐ Yes →	year	month	☐	_____
b) Rheumatic fever in the past	☐ No ☐ Yes →	year	month	☐	_____
c) Stroke/TIA	☐ No ☐ Yes →	year	month	☐	_____
d) Peripheral embolism	☐ No ☐ Yes →	year	month	☐	_____
e) Major bleeding	☐ No ☐ Yes →	year	month	☐	_____
f) Infective endocarditis	☐ No ☐ Yes →	year	month	☐	_____
g) Percutaneous valvuloplasty	☐ No ☐ Yes →	year	month	☐	_____
h) Previous heart valve surgery	☐ No ☐ Yes →	year	month	☐	_____
i) Sickle cell anaemia	☐ No ☐ Yes →	year	month	☐	_____
j) Co-existing morbidities	☐ No ☐ Yes →	year	month	☐	_____

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DataFax #164 Plate #012 Visit #002

Subject ID

Centre# Subject #

Subject Initials F M L

11. Approximate date of first referral to hospital for RHD: year month day

12. Clinical Impression: Status at the enrollment visit

a) Valve Lesions

	Absent	Present →	Mild	Moderate	Severe
			(If a clinical impression is INCLUDED by doctor)		
i) Mitral Valve					
Stenosis	☐	☐	☐	☐	☐
Regurgitation	☐	☐	☐	☐	☐
ii) Aortic Valve					
Stenosis	☐	☐	☐	☐	☐
Regurgitation	☐	☐	☐	☐	☐
iii) Tricuspid Valve					
Stenosis	☐	☐	☐	☐	☐
Regurgitation	☐	☐	☐	☐	☐
iv) Pulmonary Stenosis					
Stenosis	☐	☐	☐	☐	☐
Regurgitation	☐	☐	☐	☐	☐

	No	Yes	Unclear
b) Clinical evidence of PHT	☐	☐	☐
c) Evidence of infective endocarditis	☐	☐	☐
d) Congestive heart failure	☐	☐	☐
e) Acute rheumatic fever	☐	☐	☐

Version 2.0 2011-Mar-02

DataFax #164 Plate #013 Visit #002

Subject ID

Centre# Subject #

Subject Initials F M L

13. Most recent ECG:

a) Was an ECG performed at this visit?

☐ No → Will you be obtaining an ECG for this participant? ☐ No → *go to section 14.*

☐ Yes → *Complete sections 13.b-e when ECG obtained*

☐ Yes → *Complete section 13.b-e*

b) Date: year month day

c) Source documentation available: ☐ No ☐ Yes

d) Rhythm: ☐ Sinus ☐ Atrial fibrillation ☐ Atrial flutter ☐ Other Dysrhythmia

e) Other comments (specify): _____

14. Most Recent CXR:

a) Was a chest x-ray (CXR) performed within last 12 months?

☐ No → Will you be obtaining a CXR for this participant? ☐ No → *go to section 15.*

☐ Yes → *Complete sections 14.b-g when CXR obtained*

☐ Yes → *Complete section 14.b-g*

b) Date: year month day

c) CXR report available: ☐ No ☐ Yes

	No	Yes
d) Cardiomegaly	☐	☐
e) Pleural effusion	☐	☐
f) Pulmonary edema	☐	☐

g) Other comments (Specify): _____

Please proceed to complete Page 5 →

Version 2.0 2011-Mar-02

DataFax #164 Plate #014 Visit #002

Subject ID

Centre# Subject #

Subject Initials F M L

15. Echocardiogram

a) Was an Echocardiogram (ECHO) performed at this visit?

☐ No → Has an ECHO been scheduled for this visit? ☐ No → *Please Schedule an ECHO now...*

☐ Yes → *Complete sections 15.b-m when ECHO obtained*

☐ Yes → *Complete section 15.b-m*

Date of most recent Echo report: year month day Report available: ☐ No ☐ Yes

Valve Lesions

b) Does the patient have prosthetic valves? ☐ No ☐ Yes → If yes, please mark (X) as appropriate:

	Mechanical	Bioprosthesis	Details: (eg type or size)
Mitral	☐	☐	_____
Aortic	☐	☐	_____
Pulmonary	☐	☐	_____
Tricuspid	☐	☐	_____

c) Has the patient had an annuloplasty? ☐ No ☐ Yes → If Yes, please specify: ☐ Mitral ☐ Tricuspid

d Mitral Valve	Absent	Present →	Mild	Moderate	Severe (please refer to facing page)
Regurgitation	☐	☐	☐	☐	☐
Stenosis	☐	☐	☐	☐	☐

Please provide gradient information in section i, ii and iii below, if the Mitral valve is **prosthetic or stenotic**:

i) MVA: ☐.☐☐ cm^2

ii) End-diastolic gradient: ☐☐☐.☐☐ mmHg

iii) Mean gradient: ☐☐☐.☐☐ mmHg

Calcification ☐ No ☐ Yes

Vegetations ☐ No ☐ Yes

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DataFax #164 Plate #015 Visit #002

Subject ID

Centre# Subject #

Subject Initials F M L

f) Aortic Valve — Absent / Present → Mild / Moderate / Severe (please refer to facing page)

- Regurgitation ☐ ☐ ☐ ☐ ☐
- Stenosis ☐ ☐ ☐ ☐ ☐

Please provide gradient information in section i, ii, iii and iv below, if the Aortic valve is **prosthetic or stenotic**:

- i) Jet velocity: ☐.☐☐ m/s — iii) Mean gradient: ☐☐☐.☐☐ mmHg
- ii) Valve area : ☐.☐☐ cm^2 — iv) Peak gradient: ☐☐☐.☐☐ mmHg

Calcification ☐ No ☐ Yes

Vegetations ☐ No ☐ Yes

g) Tricuspid Valve — Absent / Present → Mild / Moderate / Severe (please refer to facing page)

- Regurgitation ☐ ☐ ☐ ☐ ☐
- Stenosis ☐ ☐ ☐ ☐ ☐

Please provide doppler gradient information below, if the Tricuspid valve is **prosthetic or stenotic**:

Doppler gradients (in mmHg): mean ☐☐☐.☐☐ End-diastolic ☐☐☐.☐☐

Calcification ☐ No ☐ Yes

Vegetations ☐ No ☐ Yes

Tricuspid valve annulus ☐☐.☐ mm

h) Pulmonary Valve — Absent / Present → Mild / Moderate / Severe (please refer to facing page)

- Regurgitation ☐ ☐ ☐ ☐ ☐
- Stenosis ☐ ☐ ☐ ☐ ☐

Please provide doppler gradient information below, if the Pulmonary valve is **prosthetic or stenotic**:

Doppler gradients (in mmHg): peak ☐☐☐.☐☐ mean ☐☐☐.☐☐

Calcification ☐ No ☐ Yes

Vegetations ☐ No ☐ Yes

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DataFax #164 Plate #016 Visit #002

Subject ID

Centre# Subject #

Subject Initials F M L

i) Pulmonary hypertension TR gradient: ☐☐.☐☐ mmHg

TR velocity: ☐☐.☐☐ m/s

j) Left ventricular dimensions LVIDd ☐☐.☐ mm

LVIDs ☐☐.☐ mm

k) Left ventricular ejection fraction: ☐☐.☐ %

l) Left ventricular shortening fraction: ☐☐.☐ %

m) Left atrium AO: ☐☐.☐ mm

LA: ☐☐.☐ mm

LA:AO ratio: ☐☐.☐☐

n) Additional echo findings:

Spontaneous echo contrast ☐ No ☐ Yes

Pericardial effusion ☐ No ☐ Yes

Left atrial thrombus ☐ No ☐ Yes → Details: _____

Size: ☐☐☐ X ☐☐☐ mm

Thrombi other than LA ☐ No ☐ Yes → Details: _____

Size: ☐☐☐ X ☐☐☐ mm

o) Further comments: _____

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DataFax #164 Plate #017 Visit #002

Subject ID

Centre# Subject #

Subject Initials F M L

16. Typical Echo features

Significant Morphological features	AND/OR	Significant Regurgitation involving 1 or more valves
☐ Leaflet thickening		☐ Seen in more than 1 plane
☐ Chordal thickening		☐ High velocity doppler > 3m/s
☐ Excessive leaflet motion		☐ Regurgitation jet length of >1cm OR Multiple jets
☐ Restricted leaflet motion		
☐ Calcification		
☐ Nodules		
☐ Vegetations		
☐ Hockey stick deformity		

17. Likelihood of RHD ☐ No ☐ Yes

Please proceed to complete Page 9 ⟶

DataFax #164 Plate #018 Visit #002

Subject ID

Centre# Subject #

Subject Initials F M L

Medication:

18. Secondary prophylaxis

a) Approximate date of commencing secondary prophylaxis: year month day → ☐ IMI ☐ P.O

b) Currently on secondary prophylaxis: ☐ No *(Please proceed to question 19)*
☐ Yes → Specify: ☐ Benzathine penicillin
☐ Oral agents

i) Benzathine penicillin dose → ☐ 4wkly ☐ 3wkly ☐ 2wkly

No. of injections received in the past year:
(According to records/ Physician's estimate)

% adherence
(See facing page for calculation) %

ii) Oral agents: (mark (x) as appropriate)

☐ Oral penicillin
(specify compound and dosage):_____

☐ Others
(specify compound and dosage):_____

No. of oral prescriptions filled in past year:
(According to Physician's estimate)

% adherence
(According to Physician's estimate) %

Please proceed to complete Page 10 →

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DataFax #164 Plate #019 Visit #002

Subject ID

Centre# Subject #

Subject Initials F M L

19. Oral anticoagulation

a) Is patient in sinus rhythm? ☐ *No* ☐ *Yes (Please proceed to question 20.)*

ECG available ☐ No ☐ Yes

If no, has oral anticoagulation been prescribed? ☐ *No* ☐ *Yes* (If yes, please provide details below)

☐ Warfarin → i) How many measurements of INR have been performed in the last 6 months?

☐ None ☐ 1-3 ☐ 4-6 ☐ >6

ii) Is patient aware of what his/her INR should be?

☐ *No*

☐ *Yes* → if yes, what is the target INR? ☐.☐☐ to ☐.☐☐

(According to patient)

iii) Last three INR values:

1- ☐.☐☐ → Dated: ☐☐☐☐ (year) ☐☐ (month) ☐☐ (day)

2- ☐.☐☐ → Dated: ☐☐☐☐ (year) ☐☐ (month) ☐☐ (day)

3- ☐.☐☐ → Dated: ☐☐☐☐ (year) ☐☐ (month) ☐☐ (day)

☐ Acenicoumalone

☐ Aspirin

☐ Others *specify:* _____

20. Other medication: (Please mark (X) as appropriate)

	No	Yes	
a) Beta-adrenergic blockers	☐	☐	
b) Calcium channel blockers	☐	☐	
c) Diuretics	☐	☐	
d) ACE inhibitors	☐	☐	
e) Antiarrhythmics	☐	☐	
f) Digoxin	☐	☐	
g) Contraceptives	☐	☐	*Specify:* _____
h) Others	☐	☐	*Specify:* _____

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DataFax #164 Plate #020 Visit #002

Subject ID

Centre# Subject #

Subject Initials F M L

21. Does the participant have Poor oro-dental hygiene: ☐ No ☐ Yes
(including dental caries, gum disease)

Completing question 22 is optional:

22. HIV Status: ☐ Negative ☐ Positive ☐ Unknown ☐ non-disclosure

Please provide details below if information available:

a) Opportunistic infections: ☐ No ☐ Yes → Details: _____

b) If HIV positive, WHO Clinical stage I-IV: ☐☐ Date of WHO staging: ☐☐☐☐ (year) ☐☐ (month) ☐☐ (day)

c) CD4 count or % at diagnosis: ☐☐☐☐ Date of diagnosis: ☐☐☐☐ (year) ☐☐ (month) ☐☐ (day)
OR ☐☐ %

d) Most recent CD4 Count or %: ☐☐☐☐ Date of CD4 count or %: ☐☐☐☐ (year) ☐☐ (month) ☐☐ (day)
OR ☐☐ %

e) ARVs: ☐ No ☐ Yes → If yes, please provide Date of commencement: ☐☐☐☐ (year) ☐☐ (month) ☐☐ (day)

f) Other comments including regime: _____

_____

Person Completing Report: _____ (Print Last Name) _____ (Initial) Date: 2 0 ☐☐ ☐☐ ☐☐

Version 2.0 2011-Mar-02

3. 12 month CRF

Global Registry of Rheumatic Heart Disease

12 Month Follow-up Questionnaire

INSTRUCTIONS

Please complete Subject's Initials on every page

F	M	L

F= first letter of first name M= first letter of middle name

L= first letter of last name

Please answer EACH question by marking an X in ONE BOX on each line: (unless otherwise instructed)

X

OR

By writing number(s) in the spaces provided:

1	8

OR

By specifying the answer on the line(s) provided

Version 2.0b - 2011 Mar 02

This data should be entered within 3 months of the enrolment date.

Q1.
If participant is unable to complete follow-up visit, complete question 1.

if participant is unable to continue participation, example if participant has moved, but willing to continue telephone participation, complete information for this visit via telephone and schedule in a call for 24 months.

If information is obtained via more than one source, e.g. telephone and records, check more than one box.

Q2. ALways recheck all contact details especially mobile phone and addresses. If there are any changes, complete the contact details report.

DataFax #164 Plate #030 Visit #003

Subject ID

Centre# Subject #

Subject Initials F M L

Visit date: year month day

1. Visit and medication adherance:

Did participant complete follow-up clinic visit? ☐ No → *If no, complete the rest of Question 1*
☐ Yes

☐ Information obtained by telephone visit → *Continue to complete the visit form*

☐ Information obtained through third party → *Date Info obtained from 3rd party* year month day
(i.e. family physician, medical records)
→ ☐ *Family Physician* ☐ *Relative or Friend* ☐ *Other(specify)* _____

☐ Refuses Further Participation → Will participant agree to telephone/mail follow-up? ☐ *Yes* → *Continue to Follow*
☐ *No* → *Complete information for this visit and contact Project Office*

☐ Lost → *Number of attempts made to contact the patient* ☐☐ *(If less than 4 attempts please attempt contact again)*
→ *Was primary contact person/relative contacted?* ☐ *Yes* ☐ *No* → *(If no, please do so)*
→ *Was primary care physician contacted?* ☐ *Yes* ☐ *No* → *(If no, please do so)*

☐ Died → *Complete and Fax Death Report*

2. Contact Information Update: Has any of the following information changed for this participant since their last visit:

	No	Yes
a) Name	☐	☐
b) Hospital #	☐	☐
c) Home Address/phone; Work Phone; Cell Phone	☐	☐
d) Primary or Secondary Contact Person	☐	☐
e) Local Physician OR Clinic	☐	☐

→ If "Yes" to any of these, please complete the "contact details report"

3. Measurements:

a) Blood Pressure Systolic ☐☐☐ / Diastolic ☐☐☐ mmHg

b) Pulse rate ☐☐☐ beats/min

c) Weight ☐☐☐.☐ kg

d) Irregular rhythm ☐ No ☐ Yes

e) Height ☐☐☐.☐ cm

Version 1.0

2011-Apr-09

4. Status at current visit:

•This section refers to status at current visit. More than one box may be checked.

•9.b NYHA classification: Refer to the Table 1 below for NYHA class codes.

Table 1: NYHA classification:

Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnoea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnoea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnoea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

DataFax #164 Plate #031 Visit #003

Subject ID

Centre# Subject #

Subject Initials F M L

4. Status at the current visit:

a) Symptoms: (please mark (X) as appropriate)

☐ Asymptomatic	☐ Chest pain	☐ Routine clinic visit
☐ Dyspnea	☐ Fever	☐ Palpitations
☐ Syncope	☐ Fatigue	☐ Other, Specify: _____

b) NYHA class → (please refer to facing page for codes)

☐ I ☐ II ☐ III ☐ IV

5. Events: (As taken from doctor's notes and patient's recollection)

	No	Yes	Number of Episodes	Report#	Report#
a) Congestive Heart Failure	☐	☐	☐	12	12
b) Stroke/TIA	☐	☐	☐	13	13
c) Hospitalization	☐	☐	☐	14	14
d) Major Bleeding	☐	☐	☐	15	15
e) infective endocarditis	☐	☐	☐	16	16
f) Prosthetic Valve Thrombosis	☐	☐	☐	17	17
g) Acute Rheumatic Fever	☐	☐	☐	18	18
h) Valvuloplasty	☐	☐	☐	20	20
i) Valve surgery	☐	☐	☐	21	21
j) Systemic embolism	☐	☐	☐	23	23
k) Atrial Fibrilation / Flutter	☐	☐	☐	22	22

6. Pregnancy: (For Women Only)

Has this participant become pregnant since her last visit? ☐ No

☐ Yes → Please complete "Pregnancy Report" 19

Version 1.0 2011-Apr-09

Q7 and Q8.

These only need to be completed if clinically indicated.

DataFax #164 Plate #013 Visit #003

Subject ID

Centre# Subject #

Subject Initials F M L

7. Most recent ECG:

a) Was an ECG performed at this visit? *(ECG is only required if clinically indicated)*

☐ No → Will you be obtaining an ECG for this participant? ☐ No → *go to section 7.*

☐ Yes → *Complete sections 6.b-e when ECG obtained*

☐ Yes → *Complete section 6.b-e*

b) Date: year month day c) Source documentation available: ☐ No ☐ Yes

d) Rhythm: ☐ Sinus ☐ Atrial fibrillation ☐ Atrial flutter ☐ Other Dysrhythmia

e) Other comments (specify): _____

8. Most Recent CXR:

a) Was a chest x-ray (CXR) performed within last 12 months? *(CXR is only required if clinically indicated)*

☐ No → Will you be obtaining a CXR for this participant? ☐ No → *go to section 8.*

☐ Yes → *Complete sections 7.b-g when CXR obtained*

☐ Yes → *Complete section 7.b-g*

b) Date: year month day c) CXR report available: ☐ No ☐ Yes

	No	Yes
d) Cardiomegaly	☐	☐
e) Pleural effusion	☐	☐
f) Pulmonary edema	☐	☐

g) Other comments (Specify): _____

Please proceed to complete Page 4 →

9. Echocardiogram:

a) An echocardiogram needs to be scheduled withing 3 months of the 12 months visit.

Valve Lesions:

b) and c) Indicate if the participant has a prosthetic valve and provide details.

d) Mitral Valve: Please use the tables below to indicate the presence and severity of Mitral regurgitation and/or stenosis.

Table 1: Mitral Stenosis

	Mild Mitral Stenosis	Moderate Mitral Stenosis	Severe Mitral Stenosis
Mitral Valve area (MVA)	1.5 to 2.5 cm^2	1.0 to 1.5 cm2	<1.0 cm2
End-diastolic pressure gradient	2 to 6 mmHg	6 to 10 mmHg	>10 mmHg
Mean Pressure gradient	<5 mmHg	6 to 10 mmHg	>10 mmHg

Table 2: Mitral Regurgitation

	Mild Mitral Regurgitation	Moderate Mitral Regurgitation	Severe Mitral Regurgitation
CW Doppler signal/jet area	Small, central jet(< 20% of LA area)	Strong complete MR spectral envelope by CW Doppler	Strong complete mitral regurgitation signal
Left atrium(LA) and left ventricular(LV) enlargement	minimal	Moderate to severe LA and LV enlargement	Moderate to severe LA and LV enlargement
Regurgitation fraction	<20%	20 to 30%	> 40% , wall-impinging jet of any size, swirling in LA

See manual of operations for the full report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1998 guidelines for the management of patients with valvular heart disease) and the classification on echo of valvular lesions.

DataFax #164 Plate #014 Visit #003

Subject ID

Centre# Subject #

Subject Initials F M L

9. Echocardiogram

a) Was an Echocardiogram (ECHO) performed at this visit?

☐ No → Has an ECHO been scheduled for this visit? ☐ No → *Please Schedule an ECHO now...*

☐ Yes → *Complete sections 8.b-m when ECHO obtained*

☐ Yes → *Complete section 8.b-m*

Date of most recent Echo report: year month day Report available: ☐ No ☐ Yes

Valve Lesions

b) Does the patient have prosthetic valves? ☐ No ☐ Yes → If yes, please mark (X) as appropriate:

	Mechanical	Bioprosthesis	Details: (eg type or size)
Mitral	☐	☐	_____
Aortic	☐	☐	_____
Pulmonary	☐	☐	_____
Tricuspid	☐	☐	_____

c) Has the patient had an annuloplasty? ☐ No ☐ Yes → If Yes, please specify: ☐ Mitral ☐ Tricuspid

d Mitral Valve	Absent	Present →	Mild	Moderate	Severe (please refer to facing page)
Regurgitation	☐	☐	☐	☐	☐
Stenosis	☐	☐	☐	☐	☐

Please provide gradient information in section i, ii and iii below, if the Mitral valve is **prosthetic or stenotic**:

i) MVA: ☐.☐☐ cm^2

ii) End-diastolic gradient: ☐☐☐.☐☐ mmHg

iii) Mean gradient: ☐☐☐.☐☐ mmHg

Calcification ☐ No ☐ Yes

Vegetations ☐ No ☐ Yes

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d)Aortic Valve: Please use the tables below to indicate the presence and severity of Aortic regurgitation and/or stenosis.

Table 1: Aortic Stenosis

	Mild Aortic Stenosis	Moderate Aortic Stenosis	Severe Aortic Stenosis
Jet Velocity	<3.0 m/s	3.0 - 4.0 m/s	> 4.0 m/s
Mean gradient	<25 mmHg	25-40 mmHg	>40 mmHg
Valve area (cm^2)	>1.5 cm^2	1.0 to 1.5 cm^2	<1.0 cm^2

Table 2: Aortic Regurgitation

	Mild Aortic Regurgitation	Moderate Aortic Regurgitation	Severe Aortic Regurgitation
CW Doppler jet width	Central jet width < 25% of LVOT	Intermediate values	Central jet width > 65% of LVOT
Left ventricular(LV) enlargement	minimal	Moderate to severe LV enlargement	Severe LV enlargement
Diastolic reversal in the descending aorta	No or brief	Intermediate values	Holodiastolic flow reversal

e)Tricuspid Valve: Please use the tables below to indicate the presence and severity of Tricuspid regurgitation and/or stenosis.

Table 3: Tricuspid Stenosis

	Mild Tricuspid Stenosis	Moderate Tricuspid Stenosis	Severe Tricuspid Stenosis
Mean gradient	<5 mmHg	Intermediate values	>5 mmHg

Table 4: Tricuspid Regurgitation

	Mild Tricuspid Regurgitation	Moderate Tricuspid Regurgitation	Severe Tricuspid Regurgitation
Hepatic vein flow	Systolic dominance	Systolic blunting	Systolic reversal

f) Pulmonary Valve: Please use the tables below to indicate the presence and severity of Pulmonary regurgitation and/or stenosis.

Table 5: Pulmonary Stenosis

	Mild Pulmonary Stenosis	Moderate Pulmonary Stenosis	Severe Pulmonary Stenosis
Jet velocity	<3 m/s	3.0 - 4.0 m/s	>4.0 m/s or maximum gradient >60 mmHg

Table 6: Pulmonary Regurgitation

	Mild Pulmonary Regurgitation	Moderate Pulmonary Regurgitation	Severe Pulmonary Regurgitation
Hepatic vein flow	Systolic dominance	Systolic blunting	Systolic reversal
RV size	Normal	Normal to Dilated	Dilated

See manual of operations for the full report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1998 guidelines for the management of patients with valvular heart disease) and the classification on echo of valvular lesions.

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f) Aortic Valve — Absent ☐ Present ☐ → Mild ☐ Moderate ☐ Severe ☐ (please refer to facing page)

Regurgitation ☐ ☐ ☐ ☐ ☐

Stenosis ☐ ☐ ☐ ☐ ☐

Please provide gradient information in section i, ii, iii and iv below, if the Aortic valve is **prosthetic or stenotic**:

i) Jet velocity: ☐.☐☐ m/s iii) Mean gradient: ☐☐☐.☐☐ mmHg

ii) Valve area : ☐.☐☐ cm^2 iv) Peak gradient: ☐☐☐.☐☐ mmHg

Calcification ☐ No ☐ Yes

Vegetations ☐ No ☐ Yes

g) Tricuspid Valve — Absent ☐ Present ☐ → Mild ☐ Moderate ☐ Severe ☐ (please refer to facing page)

Regurgitation ☐ ☐ ☐ ☐ ☐

Stenosis ☐ ☐ ☐ ☐ ☐

Please provide doppler gradient information below, if the Tricuspid valve is **prosthetic or stenotic**:

Doppler gradients (in mmHg): mean ☐☐☐.☐☐ End-diastolic ☐☐☐.☐☐

Calcification ☐ No ☐ Yes

Vegetations ☐ No ☐ Yes

h) Pulmonary Valve — Absent ☐ Present ☐ → Mild ☐ Moderate ☐ Severe ☐ (please refer to facing page)

Regurgitation ☐ ☐ ☐ ☐ ☐

Stenosis ☐ ☐ ☐ ☐ ☐

Please provide doppler gradient information below, if the Pulmonary valve is **prosthetic or stenotic**:

Doppler gradients (in mmHg): peak ☐☐☐.☐☐ mean ☐☐☐.☐☐

Calcification ☐ No ☐ Yes

Vegetations ☐ No ☐ Yes

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i) Pulmonary hypertension TR gradient: ☐☐.☐☐ mmHg

TR velocity: ☐☐.☐☐ m/s

j) Left ventricular dimensions LVIDd: ☐☐.☐ mm

LVIDs: ☐☐.☐ mm

k) Left ventricular ejection fraction: ☐☐.☐ %

l) Left ventricular shortening fraction: ☐☐.☐ %

m) Left atrium AO: ☐☐.☐ mm

LA: ☐☐.☐ mm

LA:AO ratio: ☐☐.☐☐

n) Additional echo findings:

Spontaneous echo contrast ☐ No ☐ Yes

Pericardial effusion ☐ No ☐ Yes

Left atrial thrombus ☐ No ☐ Yes → Details: _____ Size: ☐☐☐ X ☐☐☐ mm

Thrombi other than LA ☐ No ☐ Yes → Details: _____ Size: ☐☐☐ X ☐☐☐ mm

o) Further comments: _____

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Medication

10. Secondary prophylaxis

a) The date for commencing secondary prophylaxis must be completed for both, the current users and past users. If the participant has not used secondary prophylaxis in the past, or is currenly not on secondary prophylaxis, but is being put on secondary prophylaxis starting this visit, please write in today's date.

b) If a participant is not on secondary prophylaxis currently, please answer "No" and skip to section 19. For participants that are currently on secondary prophylaxis or that are beginign the secondary prophylaxis starting this visit, please answer "Yes".

If the paricipant is commencing the secondary prophylaxis at this visit, please write "0" for used in th epast year and the % medication adherence.

To calculate the percent of injections received for an individual:

* Record the number of injections PRESCRIBED for a full 12 months (e.g. the number of injections prescribed from January and December 2007 for a person on 4-weekly treatment = 13)

* Count the number of injections RECEIVED during the 12 months (e.g. 10 injections may have been received)

* Calculate: the number of injections RECEIVED (10) divided by the number PRESCRIBED (13) and multiply by 100

(10 ÷ 13) x 100 = 77%

In this example, the person received 77% of prescribed injections in 2007.

If injections were prescribed for the full year but no injections were received, record 0%.

Oral agents

To calculate the percent of oral prescriptions received for an individual:

* Record the number of medication PRESCRIBED for a full 12 months (e.g. the number of injections prescribed from January and December 2007 for a person on 4-weekly treatment = 13)

* Count the number of medication RECEIVED during the 12 months (e.g. 10 injections may have been received)

* Calculate: the number of medication RECEIVED (10) divided by the number PRESCRIBED (13) and multiply by 100

(10 ÷ 13) x 100 = 77%

In this example, the person received 77% of prescribed injections in 2007.

We are aware that this calculation may be faulty as we are not including a pill count or other means to verify oral medication.

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Subject ID

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Subject Initials F M L

Medication:

10. Secondary prophylaxis

a) Has the participant ever used secondary prophylaxis:

☐ No *(Please proceed to question 11)*

☐ Yes → Specify: ☐ Benzathine penicillin
☐ Oral agents

→ Specify: ☐ Currently on secondary prophylaxis
☐ Past use of secondary prophylaxis

b) Approximate date of commencing secondary prophylaxis: ☐☐☐☐ (year) ☐☐ (month) ☐☐ (day) → ☐ IMI ☐ P.O

i) Benzathine penicillin dose → ☐ 4wkly ☐ 3wkly ☐ 2wkly

No. of injections received in the past year: ☐☐☐
(According to records/ Physician's estimate)

% adherence ☐☐☐ %
(See facing page for calculation)

ii) Oral agents: (mark (x) as appropriate)

☐ Oral penicillin
(specify compound and dosage):_____

☐ Others
(specify compound and dosage):_____

No. of oral prescriptions filled in past year: ☐☐☐
(According to Physician's estimate)

% adherence ☐☐☐ %
(According to Physician's estimate)

Please proceed to complete Page 8 →

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DataFax #164 Plate #019 Visit #003

Subject ID

Centre# Subject #

Subject Initials F M L

11. Oral anticoagulation

a) Is patient in sinus rhythm? ☐ *No* ☐ *Yes (Please proceed to question 13.)*

ECG available ☐ No ☐ Yes

If no, has oral anticoagulation been prescribed? ☐ *No* ☐ *Yes* (If yes, please provide details below)

☐ Warfarin → i) How many measurements of INR have been performed in the last 6 months?

☐ None ☐ 1-3 ☐ 4-6 ☐ >6

ii) Is patient aware of what his/her INR should be?

☐ *No*

☐ *Yes* → if yes, what is the target INR? ☐.☐☐ to ☐.☐☐

(According to patient)

iii) Last three INR values:

1- ☐.☐☐ → Dated: ☐☐☐☐ (year) ☐☐ (month) ☐☐ (day)

2- ☐.☐☐ → Dated: ☐☐☐☐ (year) ☐☐ (month) ☐☐ (day)

3- ☐.☐☐ → Dated: ☐☐☐☐ (year) ☐☐ (month) ☐☐ (day)

☐ Acenicoumalone

☐ Aspirin

☐ Others *specify:* _____

12. Other medication: (Please mark (X) as appropriate)

	No	Yes	
a) Beta-adrenergic blockers	☐	☐	
b) Calcium channel blockers	☐	☐	
c) Diuretics	☐	☐	
d) ACE inhibitors	☐	☐	
e) Antiarrhythmics	☐	☐	
f) Digoxin	☐	☐	
g) Contraceptives	☐	☐	*Specify:* _____
h) Others	☐	☐	*Specify:* _____

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13. Does the participant have Poor oro-dental hygiene: ☐ No ☐ Yes
(including dental caries, gum disease)

Completing question 14 is optional:

14. HIV Status: ☐ Negative ☐ Positive ☐ Unknown ☐ non-disclosure

Please provide details below if information available:

a) Opportunistic infections: ☐ No ☐ Yes → Details: _____

b) If HIV positive, WHO Clinical stage I-IV: ☐☐ Date of WHO staging: ☐☐☐☐ (year) ☐☐ (month) ☐☐ (day)

c) CD4 count or % at diagnosis: ☐☐☐☐ Date of diagnosis: ☐☐☐☐ (year) ☐☐ (month) ☐☐ (day)
OR ☐☐ %

d) Most recent CD4 Count or %: ☐☐☐☐ Date of CD4 count or %: ☐☐☐☐ (year) ☐☐ (month) ☐☐ (day)
OR ☐☐ %

e) ARVs: ☐ No ☐ Yes → If yes, please provide Date of commencement ☐☐☐☐ (year) ☐☐ (month) ☐☐ (day)

f) Other comments including regime: _____

Person Completing Report: _____ (Print Last Name) _____ (Initial) Date: 2 0 ☐☐ ☐☐ ☐☐

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Global Registry of Rheumatic Heart Disease

24 Month Visit Questionnaire

INSTRUCTIONS

Please complete Subject's Initials on every page

F	M	L

F= first letter of first name **M=** first letter of middle name

L= first letter of last name

Please answer EACH question by marking an X in ONE BOX on each line: (unless otherwise instructed)

X

OR

By writing number(s) in the spaces provided:

1	8

OR

By specifying the answer on the line(s) provided

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This data should be entered within 3 months of the enrolment date.

Q1.
If participant is unable to complete follow-up visit, complete question 1.

if participant is unable to continue participation, example if participant has moved, but willing to continue telephone participation, complete information for this visit via telephone and schedule in a call for 24 months.

If information is obtained via more than one source, e.g. telephone and records, check more than one box.

Q2. ALways recheck all contact details especially mobile phone and addresses. If there are any changes, complete the contact details report.

Remedy #164 Plate #030 Visit #004

Subject ID

Centre# Subject #

Subject Initials F M L

Visit date: year month day

1. Visit and medication adherance:

Did participant complete follow-up clinic visit? ☐ No → *If no, complete the rest of Question 1*
☐ Yes

☐ Information obtained by telephone visit → *Continue to complete the visit form*

☐ Information obtained through third party → *Date Info obtained from 3rd party* year month day
(i.e. family physician, medical records)
→ ☐ *Family Physician* ☐ *Relative or Friend* ☐ *Other(specify)* _____

☐ Refuses Further Participation → Will participant agree to telephone/mail follow-up? ☐ *Yes* → *Continue to Follow*
☐ *No* → *Complete information for this visit and contact Project Office*

☐ Lost → *Number of attempts made to contact the patient* ☐☐ *(If less than 4 attempts please attempt contact again)*
→ *Was primary contact person/relative contacted?* ☐ *Yes* ☐ *No* → *(If no, please do so)*
→ *Was primary care physician contacted?* ☐ *Yes* ☐ *No* → *(If no, please do so)*

☐ Died → *Complete and Fax Death Report*

2. <u>Contact Information Update:</u> Has any of the following information changed for this participant since their last visit:

	No	Yes
a) Name	☐	☐
b) Hospital #	☐	☐
c) Home Address/phone; Work Phone; Cell Phone	☐	☐
d) Primary or Secondary Contact Person	☐	☐
e) Local Physician OR Clinic	☐	☐

→ If "Yes" to any of these, please complete the "contact details report"

3. <u>Measurements:</u>

a) Blood Pressure Systolic ☐☐☐ / Diastolic ☐☐☐ mmHg

b) Pulse rate ☐☐☐ beats/min

c) Weight ☐☐☐.☐ kg

d) Irregular rhythm ☐ No ☐ Yes

e) Height ☐☐☐.☐ cm

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4. Status at current visit:

•This section refers to status at current visit. More than one box may be checked.

•9.b NYHA classification: Refer to the Table 1 below for NYHA class codes.

Table 1: NYHA classification:

Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnoea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnoea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnoea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

Remedy #164 Plate #031 Visit #004

Subject ID

Centre# Subject #

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4. Status at the current visit:

a) Symptoms: (please mark (X) as appropriate)

☐ Asymptomatic	☐ Chest pain	☐ Routine clinic visit
☐ Dyspnea	☐ Fever	☐ Palpitations
☐ Syncope	☐ Fatigue	☐ Other, Specify: _____

b) NYHA class → (please refer to facing page for codes)

☐ I ☐ II ☐ III ☐ IV

5. Events: (As taken from doctor's notes and patient's recollection)

	No	Yes	Number of Episodes	Report#	Report#
a) Congestive Heart Failure	☐	☐	☐	12	12
b) Stroke/TIA	☐	☐	☐	13	13
c) Hospitalization	☐	☐	☐	14	14
d) Major Bleeding	☐	☐	☐	15	15
e) infective endocarditis	☐	☐	☐	16	16
f) Prosthetic Valve Thrombosis	☐	☐	☐	17	17
g) Acute Rheumatic Fever	☐	☐	☐	18	18
h) Valvuloplasty	☐	☐	☐	20	20
i) Valve surgery	☐	☐	☐	21	21
j) Systemic embolism	☐	☐	☐	23	23
k) Atrial Fibrilation / Flutter	☐	☐	☐	22	22

6. Pregnancy: (For Women Only)

Has this participant become pregnant since her last visit? ☐ No

☐ Yes → Please complete "Pregnancy Report" 19

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Q7 and Q8.

These only need to be completed if clinically indicated.

Remedy #164 Plate #013 Visit #004

Subject ID

Centre# Subject #

Subject Initials F M L

7. Most recent ECG:

a) Was an ECG performed at this visit? *(ECG is only required if clinically indicated)*

☐ No → Will you be obtaining an ECG for this participant? ☐ No → *go to section 7.*

☐ Yes → *Complete sections 6.b-e when ECG obtained*

☐ Yes → *Complete section 6.b-e*

b) Date: year month day

c) Source documentation available: ☐ No ☐ Yes

d) Rhythm: ☐ Sinus ☐ Atrial fibrillation ☐ Atrial flutter ☐ Other Dysrhythmia

e) Other comments (specify): _____

8. Most Recent CXR:

a) Was a chest x-ray (CXR) performed within last 12 months? *(CXR is only required if clinically indicated)*

☐ No → Will you be obtaining a CXR for this participant? ☐ No → *go to section 8.*

☐ Yes → *Complete sections 7.b-g when CXR obtained*

☐ Yes → *Complete section 7.b-g*

b) Date: year month day

c) CXR report available: ☐ No ☐ Yes

	No	Yes
d) Cardiomegaly	☐	☐
e) Pleural effusion	☐	☐
f) Pulmonary edema	☐	☐

g) Other comments (Specify): _____

Please proceed to complete Page 4 →

9. Echocardiogram:

a) An echocardiogram needs to be scheduled withing 3 months of the 12 months visit.

Valve Lesions:

b) and c) Indicate if the participant has a prosthetic valve and provide details.

d) Mitral Valve: Please use the tables below to indicate the presence and severity of Mitral regurgitation and/or stenosis.

Table 1: Mitral Stenosis

	Mild Mitral Stenosis	Moderate Mitral Stenosis	Severe Mitral Stenosis
Mitral Valve area (MVA)	1.5 to 2.5 cm^2	1.0 to 1.5 cm2	<1.0 cm2
End-diastolic pressure gradient	2 to 6 mmHg	6 to 10 mmHg	>10 mmHg
Mean Pressure gradient	<5 mmHg	6 to 10 mmHg	>10 mmHg

Table 2: Mitral Regurgitation

	Mild Mitral Regurgitation	Moderate Mitral Regurgitation	Severe Mitral Regurgitation
CW Doppler signal/jet area	Small, central jet(< 20% of LA area)	Strong complete MR spectral envelope by CW Doppler	Strong complete mitral regurgitation signal
Left atrium(LA) and left ventricular(LV) enlargement	minimal	Moderate to severe LA and LV enlargement	Moderate to severe LA and LV enlargement
Regurgitation fraction	<20%	20 to 30%	> 40% , wall-impinging jet of any size, swirling in LA

See manual of operations for the full report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1998 guidelines for the management of patients with valvular heart disease) and the classification on echo of valvular lesions.

Remedy #164 Plate #014 Visit #004

Subject ID

Centre# Subject #

Subject Initials F M L

9. Echocardiogram

a) Was an Echocardiogram (ECHO) performed at this visit?

☐ No → Has an ECHO been scheduled for this visit? ☐ No → *Please Schedule an ECHO now...*

☐ Yes → *Complete sections 8.b-m when ECHO obtained*

☐ Yes → *Complete section 8.b-m*

Date of most recent Echo report: ☐☐☐☐ (year) ☐☐ (month) ☐☐ (day) Report available: ☐ No ☐ Yes

Valve Lesions

b) Does the patient have prosthetic valves? ☐ No ☐ Yes → If yes, please mark (X) as appropriate:

	Mechanical	Bioprosthesis	Details: (eg type or size)
Mitral	☐	☐	_____
Aortic	☐	☐	_____
Pulmonary	☐	☐	_____
Tricuspid	☐	☐	_____

c) Has the patient had an annuloplasty? ☐ No ☐ Yes → If Yes, please specify: ☐ Mitral ☐ Tricuspid

d Mitral Valve	Absent	Present →	Mild	Moderate	Severe (please refer to facing page)
Regurgitation	☐	☐	☐	☐	☐
Stenosis	☐	☐	☐	☐	☐

Please provide gradient information in section i, ii and iii below, if the Mitral valve is **prosthetic or stenotic**:

i) MVA: ☐.☐☐ cm^2

ii) End-diastolic gradient: ☐☐☐.☐☐ mmHg

iii) Mean gradient: ☐☐☐.☐☐ mmHg

Calcification ☐ No ☐ Yes

Vegetations ☐ No ☐ Yes

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d)Aortic Valve: Please use the tables below to indicate the presence and severity of Aortic regurgitation and/or stenosis.

Table 1: Aortic Stenosis

	Mild Aortic Stenosis	Moderate Aortic Stenosis	Severe Aortic Stenosis
Jet Velocity	<3.0 m/s	3.0 - 4.0 m/s	> 4.0 m/s
Mean gradient	<25 mmHg	25-40 mmHg	>40 mmHg
Valve area (cm^2)	>1.5 cm^2	1.0 to 1.5 cm^2	<1.0 cm^2

Table 2: Aortic Regurgitation

	Mild Aortic Regurgitation	Moderate Aortic Regurgitation	Severe Aortic Regurgitation
CW Doppler jet width	Central jet width < 25% of LVOT	Intermediate values	Central jet width > 65% of LVOT
Left ventricular(LV) enlargement	minimal	Moderate to severe LV enlargement	Severe LV enlargement
Diastolic reversal in the descending aorta	No or brief	Intermediate values	Holodiastolic flow reversal

e)Tricuspid Valve: Please use the tables below to indicate the presence and severity of Tricuspid regurgitation and/or stenosis.

Table 3: Tricuspid Stenosis

	Mild Tricuspid Stenosis	Moderate Tricuspid Stenosis	Severe Tricuspid Stenosis
Mean gradient	<5 mmHg	Intermediate values	>5 mmHg

Table 4: Tricuspid Regurgitation

	Mild Tricuspid Regurgitation	Moderate Tricuspid Regurgitation	Severe Tricuspid Regurgitation
Hepatic vein flow	Systolic dominance	Systolic blunting	Systolic reversal

f) Pulmonary Valve: Please use the tables below to indicate the presence and severity of Pulmonary regurgitation and/or stenosis.

Table 5: Pulmonary Stenosis

	Mild Pulmonary Stenosis	Moderate Pulmonary Stenosis	Severe Pulmonary Stenosis
Jet velocity	<3 m/s	3.0 - 4.0 m/s	>4.0 m/s or maximum gradient >60 mmHg

Table 6: Pulmonary Regurgitation

	Mild Pulmonary Regurgitation	Moderate Pulmonary Regurgitation	Severe Pulmonary Regurgitation
Hepatic vein flow	Systolic dominance	Systolic blunting	Systolic reversal
RV size	Normal	Normal to Dilated	Dilated

See manual of operations for the full report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1998 guidelines for the management of patients with valvular heart disease) and the classification on echo of valvular lesions.

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Subject ID

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f) Aortic Valve | Absent | Present → Mild | Moderate | Severe (please refer to facing page)

Regurgitation ☐ ☐ ☐ ☐ ☐

Stenosis ☐ ☐ ☐ ☐ ☐

Please provide gradient information in section i, ii, iii and iv below, if the Aortic valve is **prosthetic or stenotic**:

↳ i) Jet velocity: ☐.☐☐ m/s iii) Mean gradient: ☐☐☐.☐☐ mmHg

ii) Valve area : ☐.☐☐ cm^2 iv) Peak gradient: ☐☐☐.☐☐ mmHg

Calcification ☐ No ☐ Yes

Vegetations ☐ No ☐ Yes

g) Tricuspid Valve | Absent | Present → Mild | Moderate | Severe (please refer to facing page)

Regurgitation ☐ ☐ ☐ ☐ ☐

Stenosis ☐ ☐ ☐ ☐ ☐

Please provide doppler gradient information below, if the Tricuspid valve is **prosthetic or stenotic**:

↳ Doppler gradients (in mmHg): mean ☐☐☐.☐☐ End-diastolic ☐☐☐.☐☐

Calcification ☐ No ☐ Yes

Vegetations ☐ No ☐ Yes

h) Pulmonary Valve | Absent | Present → Mild | Moderate | Severe (please refer to facing page)

Regurgitation ☐ ☐ ☐ ☐ ☐

Stenosis ☐ ☐ ☐ ☐ ☐

Please provide doppler gradient information below, if the Pulmonary valve is **prosthetic or stenotic**:

↳ Doppler gradients (in mmHg): peak ☐☐☐.☐☐ mean ☐☐☐.☐☐

Calcification ☐ No ☐ Yes

Vegetations ☐ No ☐ Yes

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Subject ID

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i) Pulmonary hypertension TR gradient: ☐☐.☐☐ mmHg

TR velocity: ☐☐.☐☐ m/s

j) Left ventricular dimensions LVIDd: ☐☐.☐ mm

LVIDs: ☐☐.☐ mm

k) Left ventricular ejection fraction: ☐☐.☐ %

l) Left ventricular shortening fraction: ☐☐.☐ %

m) Left atrium AO: ☐☐.☐ mm

LA: ☐☐.☐ mm

LA:AO ratio: ☐☐.☐☐

n) Additional echo findings:

Spontaneous echo contrast ☐ No ☐ Yes

Pericardial effusion ☐ No ☐ Yes

Left atrial thrombus ☐ No ☐ Yes → Details: _____ Size: ☐☐☐ X ☐☐☐ mm

Thrombi other than LA ☐ No ☐ Yes → Details: _____ Size: ☐☐☐ X ☐☐☐ mm

o) Further comments: _____

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Medication

10. Secondary prophylaxis

a) The date for commencing secondary prophylaxis must be completed for both, the current users and past users. If the participant has not used secondary prophylaxis in the past, or is currenly not on secondary prophylaxis, but is being put on secondary prophylaxis starting this visit, please write in today's date.

b) If a participant is not on secondary prophylaxis currently, please answer "No" and skip to section 19. For participants that are currently on secondary prophylaxis or that are beginign the secondary prophylaxis starting this visit, please answer "Yes".

If the paricipant is commencing the secondary prophylaxis at this visit, please write "0" for used in th epast year and the % medication adherence.

To calculate the percent of injections received for an individual:

* Record the number of injections PRESCRIBED for a full 12 months (e.g. the number of injections prescribed from January and December 2007 for a person on 4-weekly treatment = 13)

* Count the number of injections RECEIVED during the 12 months (e.g. 10 injections may have been received)

* Calculate: the number of injections RECEIVED (10) divided by the number PRESCRIBED (13) and multiply by 100

(10 ÷ 13) x 100 = 77%

In this example, the person received 77% of prescribed injections in 2007.

If injections were prescribed for the full year but no injections were received, record 0%.

Oral agents

To calculate the percent of oral prescriptions received for an individual:

* Record the number of medication PRESCRIBED for a full 12 months (e.g. the number of injections prescribed from January and December 2007 for a person on 4-weekly treatment = 13)

* Count the number of medication RECEIVED during the 12 months (e.g. 10 injections may have been received)

* Calculate: the number of medication RECEIVED (10) divided by the number PRESCRIBED (13) and multiply by 100

(10 ÷ 13) x 100 = 77%

In this example, the person received 77% of prescribed injections in 2007.

We are aware that this calculation may be faulty as we are not including a pill count or other means to verify oral medication.

Remedy#164 Plate #032 Visit #004

Subject ID

Centre# Subject #

Subject Initials F M L

Medication:

10. Secondary prophylaxis

a) Has the participant ever used secondary prophylaxis:

☐ No *(Please proceed to question 11)*

☐ Yes → Specify: ☐ Benzathine penicillin
☐ Oral agents

→ Specify: ☐ Currently on secondary prophylaxis
☐ Past use of secondary prophylaxis

b) Approximate date of commencing secondary prophylaxis: ☐☐☐☐ (year) ☐☐ (month) ☐☐ (day) → ☐ IMI ☐ P.O

i) Benzathine penicillin dose → ☐ 4wkly ☐ 3wkly ☐ 2wkly

No. of injections received in the past year: ☐☐☐
(According to records/ Physician's estimate)

% adherence ☐☐☐ %
(See facing page for calculation)

ii) Oral agents: (mark (x) as appropriate)

☐ Oral penicillin
(specify compound and dosage):_____

☐ Others
(specify compound and dosage):_____

No. of oral prescriptions filled in past year: ☐☐☐
(According to Physician's estimate)

% adherence ☐☐☐ %
(According to Physician's estimate)

Please proceed to complete Page 8 →

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Remedy #164 Plate #019 Visit #004

Subject ID

Centre# Subject #

Subject Initials F M L

11. Oral anticoagulation

a) Is patient in sinus rhythm? ☐ *No* ☐ *Yes (Please proceed to question 13.)*

ECG available ☐ No ☐ Yes

If no, has oral anticoagulation been prescribed? ☐ *No* ☐ *Yes* (If yes, please provide details below)

☐ Warfarin → i) How many measurements of INR have been performed in the last 6 months?

☐ None ☐ 1-3 ☐ 4-6 ☐ >6

ii) Is patient aware of what his/her INR should be?

☐ *No*

☐ *Yes* → if yes, what is the target INR? ☐.☐☐ to ☐.☐☐

(According to patient)

iii) Last three INR values:

1- ☐.☐☐ → Dated: ☐☐☐☐ (year) ☐☐ (month) ☐☐ (day)

2- ☐.☐☐ → Dated: ☐☐☐☐ (year) ☐☐ (month) ☐☐ (day)

3- ☐.☐☐ → Dated: ☐☐☐☐ (year) ☐☐ (month) ☐☐ (day)

☐ Acenicoumalone

☐ Aspirin

☐ Others *specify:* _____

12. Other medication: (Please mark (X) as appropriate)

	No	Yes	
a) Beta-adrenergic blockers	☐	☐	
b) Calcium channel blockers	☐	☐	
c) Diuretics	☐	☐	
d) ACE inhibitors	☐	☐	
e) Antiarrhythmics	☐	☐	
f) Digoxin	☐	☐	
g) Contraceptives	☐	☐	*Specify:* _____
h) Others	☐	☐	*Specify:* _____

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Remedy #164 Plate #020 Visit #004

Subject ID

Centre# Subject #

Subject Initials F M L

13. Does the participant have Poor oro-dental hygiene: ☐ No ☐ Yes
(including dental caries, gum disease)

Completing question 14 is optional:

14. HIV Status: ☐ Negative ☐ Positive ☐ Unknown ☐ non-disclosure

Please provide details below if information available:

a) Opportunistic infections: ☐ No ☐ Yes → Details: _____

b) If HIV positive, WHO Clinical stage I-IV: ☐☐ Date of WHO staging: ☐☐☐☐ year ☐☐ month ☐☐ day

c) CD4 count or % at diagnosis: ☐☐☐☐ Date of diagnosis: ☐☐☐☐ year ☐☐ month ☐☐ day
OR ☐☐ %

d) Most recent CD4 Count or %: ☐☐☐☐ Date of CD4 count or %: ☐☐☐☐ year ☐☐ month ☐☐ day
OR ☐☐ %

e) ARVs: ☐ No ☐ Yes → If yes, please provide Date of commencement ☐☐☐☐ year ☐☐ month ☐☐ day

f) Other comments including regime: _____

Person Completing Report: _____ Print Last Name _____ Initial Date: 2 0 ☐☐ ☐☐ ☐☐

Version 1.0 2011-Aug-01

5. Death CRF

Global Registry of Rheumatic Heart Disease

Death Report

INSTRUCTIONS

Please complete Subject's Initials on every page

F	M	L

F= first letter of first name **M=** first letter of middle name

L= first letter of last name

Please answer EACH question by marking an X in ONE BOX on each line: (unless otherwise instructed)

X

OR

By writing number(s) in the spaces provided:

1	8

OR

By specifying the answer on the line(s) provided

Version 1.0- 01 Aug 2011

DEATH REPORT

DataFax #164 Plate #099 Visit #099

Subject ID

Centre# Subject #

Subject Initials F M L

1. Date of death: 2 0 ☐☐ (year) ☐☐ (month) ☐☐ (day)

2. Death witnessed: ☐ No ☐ Yes

3. Primary Cause of Death (check (X) one box only)

- ☐ Congestive heart failure
- ☐ Stroke/TIA
- ☐ Acute rheumatic fever
- ☐ Systemic embolism
- ☐ Infective endocarditis
- ☐ Valve surgery
- ☐ Pregnancy related
- ☐ Major bleeding

→ Complete corresponding event report and enter report # ☐☐☐☐

- ☐ Pulmonary embolism
- ☐ Sickle-cell disease
- ☐ Tuberculosis
- ☐ Trauma
- ☐ Cancer-specify: _____
- ☐ Other - specify: _____

4. Did patient die in hospital:

☐ No → Please provide the clinical details of cause of death below*

☐ Yes → Was the participant hospitalized for 24 hours or more?

- ☐ No → Please provide the clinical details of cause of death below*
- ☐ Yes → Complete hospitalization report and enter the report # ☐☐☐☐

*Clinical details of cause of death: _____

Please check appropriate box(es) to indicate supporting documentation retained:

- ☐ Death Certificate
- ☐ Autopsy
- ☐ Emergency department report
- ☐ Other - specify: _____

Person Completing Report: _____ Date: 2 0 ☐☐ ☐☐ ☐☐

Print last name/first initial ***Signature***

INTERNATIONAL JOURNAL OF CARDIOLOGY

AUTHOR INFORMATION PACK

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The *International Journal of Cardiology* is devoted to **cardiology** in the broadest sense. Both basic research and clinical papers can be submitted. The journal serves the interest of both practicing clinicians and researchers.

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INTRODUCTION

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