

The Economic Impact of Rheumatic Heart Disease (RHD) on the Health System of South Africa. A Cost of Illness Study.

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Declaration

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Abstract

Background

Rheumatic heart disease (RHD) is an inflammation to the heart that occurs as a complication of acute rheumatic fever (ARF), and it may result in permanent damage to the heart valves. RHD is caused by repeated events of ARF, resulting into damaged heart valves. Subsequently preventing the heart from pumping blood efficiently by putting excessive strain on the heart. Though, RHD is a disease of poverty, it is neglected in developing countries, including South Africa. Lack of adequate evidence regarding the cost of RHD has hindered national and international actions to prevent RHD related mortality. The objective of this study was to estimate the cost of RHD-related health services in a tertiary hospital in the Western Cape, South Africa.

Methods

A combination of ingredients and step-down costing approaches were used to estimate the annual cost of RHD care from health system perspective. All costs were estimated in 2017 (base year) South African Rand (ZAR) and 3% discount rate to allow depreciation and opportunity cost. Data on service utilization rates were collected using a randomly selected sample of 100 patient medical records from the Global Rheumatic Heart Disease Registry (the REMEDY study), a registry of individuals living with RHD. Patient-level clinical data, including, prices and quantities of medications and laboratory tests, were collected from Groote Schuur Hospital (GSH). Step-down costing was used to estimate provider time costs and all other facility costs such as overheads. REMEDY study and Groote Schuur Hospital (GSH) data were aggregated to estimate the total annual costs of RHD care at GSH and the average annual per-patient cost among REMEDY study participants. One-way univariate sensitivity analysis was conducted to deal with uncertainty.

Results

The total cost of RHD care at GSH was estimated at \$2, 238, 294 (ZAR 27 million) in 2017, with surgery costs accounting for 65% of total costs. Per-patient average annual costs, which included outpatient care, cardiac medical and intensive care unit (ICU) care, cardiac

catheterisation lab procedures, and heart valve surgery, was estimated at \$4, 311 (ZAR 52, 000) per-patient annually. The cost of medications and consumables related to cardiac catheterisation and heart valve surgery were the main cost drivers.

Conclusion

RHD care consumes a significant level of tertiary hospital resources in South Africa, with annual per-patient costs much higher than many other non-communicable and infectious diseases. This analysis supports the scaling up of primary and secondary prevention programmes at primary health to reduce the future burden on tertiary services. The study may also inform resource allocation efforts related to RHD at tertiary and provide cost estimates for future studies of intervention cost-effectiveness.

Keywords

Unit cost, cost analysis, health systems, provider cost, rheumatic fever, rheumatic heart disease, surgery, tertiary care, cardiology

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List of abbreviations

ARF- Acute Rheumatic Fever

CA- Cost Analysis

CEA- Cost Effectiveness Analysis

CBA- Cost Benefit Analysis

CUA- Cost Utility Analysis

GSH- Groote Schuur Hospital

ICU- Intensive care unit

NCDs- Non-communicable diseases

NGOs- Non-Governmental organisations

RHD- Rheumatic heart disease

SSA- Sub-Saharan Africa

WHO- World Health Organisations

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PART A: PROTOCOL

1. Background

Globally, cardiovascular diseases (CVDs) are the foremost contributors to the rising cost burden to health systems. A significant literature has established that the epidemiology of CVDs differs broadly depending on the resource level of the setting. Resource-poor settings are believed to account for over 80% of the world's mortality related to CVD (Bonow et al., 2002; Koech & Ngeno, 2014). Resource-poor African countries have a high prevalence of CVDs, and these CVDs are the second most common cause of mortality after infectious diseases (Koech & Ngeno, 2014). One preventable and treatable form of CVD that is especially important in Africa is rheumatic heart disease (RHD).

Rheumatic heart disease (RHD) is a disease of poverty, mainly occurring in children and young adults who have been affected by acute rheumatic fever (ARF), which in itself is a result of untreated group A streptococcal sore throat (Watkins et al., 2016). Recurrences of ARF result in RHD, where one or more heart valves are damaged by inflammation (Marion et al., 2012). Once individual's heart is affected in such a manner, the heart valves will fail to function effectively. RHD is thus a major cause of sequelae such as heart failure, as well as arrhythmias, stroke, and infective endocarditis (Watkins, 2015). All these sequelae can affect young school-going children and economically dynamic and childbearing adults (Araujo, Goulet & Meira, 2012). The condition leads to gradual disability, loss of quality of life, and eventually premature death (Kumar & Tandon, 2013). Performing heart surgery to repair or replace the valve (or valves) can minimize these challenges and prolong life, yet its cost is very high (Carapetis, Mayosi & Kaplan, 2006; Hewitson & Zilla, 2010).

Most recent estimates indicate that there are 33 million people who suffer from RHD globally, with about 320,000 deaths in 2015 (Naghavi et al. 2015; GBD¹, 2015). Predictably, RHD prevalence is high in low and middle-income countries (LMICs) (Marion et al 2012; Cilliers, 2015), especially in South Asia, Latin America, the Middle East, and Sub-Saharan Africa (Mayosi, 2010; Seckeler & Hoke, 2011). Sub-Saharan Africa, which is home for only 10% of the world's population, is thought to account for 50% of children who suffer from RHD (Ntusi & Mayosi, 2009). Studies have found that one in five African children with RHD die by the age of 15 years, and about 4 in 5 of them die by the age of 25 (Kimbally-Kaky et al. 2002; Oli &

¹ The Global Burden of Disease 2015 Study.

Asmera, 2004). School based studies in Sub-Saharan Africa indicate that the RHD prevalence in children is as high as 30 per thousand, e.g., in Mozambique (Marijon, 2007). Yet there are few studies on the epidemiology of RHD in sub-Saharan Africa, including South Africa. One recent initiative to assess non-fatal outcomes of individuals with RHD is the REMEDY² study (Engel, 2012).

However, South Africa's RHD problem is 25 times higher than the rate acknowledged as minimum by the World Health Organisation (WHO) (Health Systems Trust, 2015). In 2010, the incidence of new RHD cases among individuals over 14 years in Soweto, South Africa was 24 per 100,000 per year (Mayosi, 2010). A systematic review published by Zühlke et al. (2015), indicated that mortality caused by acute heart failure due to RHD was 25% at 60 days and 35% at 180 days. However among patients undergoing surgery, postoperative mortality was 2% at 30 days, and survival was 70% at 10 years, demonstrating that surgery, while expensive, can be a very effective intervention for RHD. On the other hand, study by Cilliers (2014) working in Soweto reported that number of children documented to have ARF and RHD has declined from 64 in 1993 to 3 in 2010. These observations highlight that while the condition persists in South Africa, health outcomes are improving, undoubtedly because of improvements in socioeconomic conditions and available better access to primary health care (including surgical facilities) (Cilliers, 2014; Zühlke et al 2015). Still, improved access to medical and surgical treatment for prevalent cases also means high costs to the health system for providing chronic care.

2. Problem Statement

Even though South Africa is categorised as a middle income country, its healthcare system has been crippled by a heavy burden of disease including HIV/AIDS, TB, maternal and child mortality, as well as non-communicable diseases and injuries (Pereira, 2014). The pre-1994 apartheid era created policies which were subjected to racial segregation resulting in dramatic health inequalities (Coovadia et al., 2009). Even now, the majority of the country's households receive low-quality education and healthcare, with many restricted to

²REMEDY study is global rheumatic heart disease registry that collects detailed data on clinical and echocardiographic features both at presentation and follow-up, and accurately document clinical and echocardiographic progression of disease and the occurrence of disease-related adverse events, and based in Groote Schuur and Red cross hospital, Cape Town South Africa" (Karthikeyan et al., 2012, Page 538).

impoverished living conditions and areas (Armstrong, 2006; Coovadia et al. 2009). These households are among the most vulnerable to diseases of poverty such as RHD (Hewitson & Zilla, 2010). The current Government of South Africa is in principle committed to health care equity and to addressing preventable infectious and non-communicable diseases. Yet RHD control does not appear to be a major priority on the Government's agenda, despite its potential cost to the healthcare system and the loss of human capital due to disability and premature mortality. Unfortunately, little is known about the cost of RHD care from the perspective of the South African Government, which limits the public sector's ability to allocate resources and assess new RHD technologies and interventions through comparative cost-effectiveness analyses (Irlam et al., 2015).

3. Objectives of the Study

The overall aim of this study is to quantify cost of care for RHD from the public health system (provider) perspective. In addition, this study will discuss the experience of the Department of Health (DoH), South Africa, since the 2005 Drakensberg Declaration on the control of Rheumatic Fever and Rheumatic Heart Diseases in the world. This declaration asserted that RF and RHD comprised greater portions of CVDs in women and children in the LMICs yet continued to remain largely neglected in the prevention efforts (Mayosi et al., 2006; Watkins et al., 2009). The specific objectives are:

- estimating the average total cost of providing RHD care for patients in the public sector with sum of representative sample from Groote Schuur Hospital (GSH) using standardised costing tools and utilisation rate
- quantifying variation in costs according to clinical characteristics
- ascertaining whether South Africa's health system (DoH) is/was equipped and prepared to engage/control RHD using data on patients diagnosed with RHD at Groote Schuur Hospital (GSH) in Cape Town.

4. Mini Literature Review

4.1 Epidemiology of RHD

RHD is a lifelong illness that results in premature death for many who are affected. A 1994 report estimated that about 12 million people suffered from RHD globally, and about 3 million of them experienced heart failure that needed frequent hospitalisation (WHO, 1994; Murray & Lopez, 1996). Many of these individuals needed costly cardiac valve surgery in interval of 5 and 10 years (WHO, 1994; Murray & Lopez, 1996; WHO, 1997).

Recent research estimates indicate that RHD remains a major global public health challenge, affecting about 33 million people across the globe with estimated 3.6 million being children between 5 and 14 years of age living in developing countries (Vos et al., 2016). The mortality rate varies between continents. For instance, in 2000, the mortality rate in Latin America was 1.8/100,000 people compared to 7.6/100,000 people in South-East Asia (Murray & Lopez, 1996; WHO, 2001). In addition, the mortality rate was noted as 0.5/100,000 people to 8.2/100,000 people in Denmark and China, respectively, while in the year 2000, about 332,000 deaths were estimated globally (WHO, 2001). That same study estimated disability-adjusted life year (DALY) rates of 27.4/100,000 to 173.4/100,000 per year (WHO, 2001).

Studies estimate that between 1.8 and 2.4 million African children suffer from RHD (Mayosi et al., 2006; Vos et al., 2016). RHD accounts for a major proportion of all cardiovascular diseases (CVDs) in children and young adults in African countries (Mayosi et al., 2006). The African continent has some of the highest prevalence rates of RHD globally. For example, among school-going children, 30 per 1000 were affected in Mozambique in 2007 and 15 per 1000 were affected in Uganda in 2012 (Guilherme et al., 2007; Kennedy and Miller, 2013). The main socioeconomic determinants of RHD include poverty, overcrowding, low educational level, unemployment, malnutrition and ill equipped health systems (Longo-Mbenza et al., 1998; Marijon et al., 2012). As a result, many LMICs still experience RHD at high rates, with its attendant economic burden, while wealthy nations have witnessed major declines in ARF and RHD over the past decades (Mishra, 2007). Several studies have established that the reason for the observed decline in RHD prevalence in developed countries included improved living conditions, presence of reliable primary health services

(especially to treat sore throat and prevent ARF), and advances in treatment for RHD such as valve surgery (Brahmadathan, 2006; Mishra, 2007; Watkins et al., 2016).

4.2 Economic Burden of RHD

Globally, little is known about the economic costs of RHD either from the health system or patient perspectives. The cost of treatment appears to vary from region to region. This is synonymous with the findings by Terreri et al. (2001). For instance, per-patient cost of care in United States of America (USA) was about \$6000 in 2002 (Saslaw et al., 1965; Ehrlich et al., 2002), while per-patient cost in China was about \$4700 in 2012 (Wang et al. 2015). One study in Cuba indicated that the cost of severe RHD care was about \$6300 (Watkins et al., 2015) in the 1990s, while the cost burden per-patient in South Africa for only inpatient treatment was \$2900 (about ZAR35, 000) in 2010 (Irlam et al., 2013).

Developed countries face the highest per-patient cost of RHD given that these countries have higher prices and greater utilisation of advanced medical care than the LMICs. At the same time, the economic impact of RHD is felt more to LMICs health systems because of the much higher numbers of cases and more limited resources. Most African children and adults with RHD have lost opportunities for prevention because of low resource allocation towards preventive interventions such as treatment of sore throat (Cilliers, 2015). The consequence of this misallocation to patients and health systems is the high cost of irreversible heart valve damage that can only be alleviated by surgery, if it is available at all (Gunter, Asmera & Parry, 2006; Watkins et al., 2016).

In addition to its cost to health systems, RHD probably affects households due to catastrophic and impoverishment impact resulting from high out-of-pocket payments to access care. Globally, over 100 million individuals are pushed into poverty and more than 150 million individuals suffer from excessive out-of-pocket healthcare payments (WHO, 2013). Cardiovascular diseases, which are generally a low priority for public finance in many countries, tend to result in catastrophic health expenditures at very high rates (Huffman et al., 2011). Yet we have very little direct evidence for the economic impact of RHD on patients, with only one study to date (in Brazil) devoted to this topic (Terreri et al., 2001). Hence in countries where the health system is ill equipped and under-financed, RHD can reinforce the

“poverty trap” by incapacitating poor people with high out-of-pocket payments (McIntyre et al., 2006). In addition, many school age children drop out of school as a result of RHD, including 67% of affected children in Nigeria (Yilgwan, Olge & Bode-Thomas, 2014). These factors can, in turn, hamper economic growth and development (Robertson & Mayosi, 2008).

4.3 Health Systems and RHD

The high medical costs of RHD, including heart surgery, leave many people without access to needed care (Gunter, Asmera & Parry, 2006; Wang et al. 2015). Additionally, health systems in LMICs are often unable to deliver RHD prevention and treatment interventions at acceptable coverage rates (Moloi et al., 2016). Prevalent barriers to care include inadequate community awareness, limited health literacy, insufficient health-seeking conduct, and absence of health care treatment options that are available, affordable and acceptable (Zuhlke et al., 2015; Moloi et al., 2016). Given these barriers and budgetary constraints, it is crucial for public health systems to address these constraints in a contextualised and economically efficient manner (Longenecker et al., 2014).

Given that RHD affects the poor, the cost burden often falls on the government to provide health services in public facilities – for instance, to 80% of the population in South Africa (Koch, 2011; Ataguba, 2012). Yet RHD treatment is very expensive; one group estimated the cost of replacing one heart valve at \$4, 145 (ZAR50, 000) (The heart and stroke foundation South Africa, 2016). Furthermore, individuals who have undergone surgery face additional challenges that may require more heart operations, making them more susceptible to complex, lifelong heart problems and their attendant costs (Marijon et al., 2012). These challenges have probably forced public health facilities to limit the number of valve surgeries that can be performed. As a consequence, many South Africans die while awaiting valve surgery (Zilla, 2014). Again, many of these costs can be prevented by increasing coverage of sore throat and ARF interventions and thus preventing RHD; in Cuba, expenditure on heart surgery fell by about 90% within a decade following a comprehensive RHD prevention program (Watkins et al., 2015).

4.4 Cost Analysis

Full economic evaluation comprises four types of approaches: cost-effectiveness analysis (CEA), cost-utility analysis (CUA), cost-benefit analysis (CBA) and cost minimisation analysis (CMA) (Drummond et al., 2005). It is often defined as a systematic approach, which is utilised to compare and contrast two or more interventions on a basis of costs and outcomes (Drummond et al., 2005). Other economic analyses only deal with the initial (first) section of an economic evaluation; these are called cost analyses (Creese & Parker, 1994). The cost analysis approach is often used in disease-specific studies to assess the cost of providing health care. On the other hand, the cost analysis approach does not assess outcomes, so it is considered as partial economic analysis approach (Creese & Parker, 1994; Drummond et al., 2005). When there are no data on interventions for a specific disease, researchers and policy makers can use cost analysis, particularly in areas that have not been explored before. A cost analysis of RHD in South Africa, for instance, may spur greater interest on the part of Government in developing interventions, and the costs can also serve as inputs for future economic evaluations.

The literature on the cost of adult cardiovascular diseases (CVDs) is much larger than the literature on RHD that was reviewed above. Studies have generally been conducted from the perspective of the patient or of the health system; recently Jaspers et al. (2015) reviewed the former, and Brouwer et al. (2015) reviewed the latter. Of note, the combined perspective of all parties, including both patients and providers, is referred to as the “societal” perspective, yet few CVD costing studies in LMICs have combined the two perspectives.

Costs can also be decomposed into direct and indirect components. Drug costs, Laboratory test costs, and consultation fees are examples of direct components, whereas time off work due to illness is an example of an indirect cost (Drummond et al. 2005). Studies of costs from the health system perspective typically do not consider indirect costs, which are largely borne by patients. Provider costs are commonly obtained from assessing medical records to understand the quantities of resources typically required to deliver care (Ivanova et al., 2009) and surveying health facilities to capture prices of all healthcare inputs (Hendriks et al., 2014).

When performing disease-specific cost of care, cost items can be valued using two approaches: ingredients (bottom-up) and top-down. Which approach to use is a key decision in costing that affects the costs and the resources required to conduct the study (Cunnama et al., 2016). The ingredients approach uses detailed action and input utilisation data from records (or observed utilisation) to estimate unit costs at the service provider level (Batura et al., 2014; Cunnama et al., 2016). The step-down approach uses formulae that allocate overall expenditure to each and every input/ingredient to determine unit costs (Cunnama et al., 2016).

Studies comparing both costing approaches suggest that the ingredients approach is likely to be more precise because it captures resources more comprehensively (Hendriks et al., 2014). The data needed for the ingredients approach can be easier for access compared to the step-down approach, even though the former is specific to a setting, more time demanding, and more expensive to carry out (Simoens, 2009). A study based in the United States further analysed importance of both costing approaches and highlighted strength of either approach. The study established that ingredients approach was better able to capture site-level differences, whereas the step-down approach was better able to capture national long run average costs (Chapko et al., 2009; Cunnama et al., 2016).

5. Study Methods

5.1 Study Design

This study will be a cost analysis of RHD from the provider (health system) perspective using a combination of bottom-up and step-down costing, similar to other studies (settumba et al., 2015). This will be a cross-sectional study that seeks to assess the average total cost of care in the Western Cape based on a typical patient mix at referral healthcare facility. All costs will be estimated in 2017 South African Rand (ZAR).

5.2 Study Setting

The study will sample patients receiving care for RHD at the Groote Schuur Hospital (GSH), situated in Cape Town, Western Cape, South Africa. Particularly, patients will be recruited from the REMEDY registry database that collects detailed data on clinical and

echocardiographic features both at presentation and follow-up with a total of about 500 study participant patients.

5.3 Sample Size

This study is cost analysis from the health system perspective at tertiary level. A random sample of 100 patient medical records from REMEDY study participants will be used for the study. We aim to estimate cost of advanced tertiary level provision of RHD treatment using the entire sample size (100 patients).

Given that the proposed study is in its pilot phase, we plan to recruit more participants in the sample if we are underpowered or need greater precision in any particular estimates. A previous study estimated the cost of average inpatient³ RHD care as \$2900 (ZAR35 000) with a variance of \$800 (+/- 25% or so) (Irlam et al 2013). We therefore assume that a sample of 100 patients will provide a 5% margin of error on the estimated mean cost and will likely be adequate for estimating the total cost of care as proclaimed by Irlam et al (2013).

6. Assessing RHD Costs from the Health System Perspective

In this study we will categorize and quantify health system-related costs of RHD to answer the question, “What is the average cost of providing RHD care in current practice?” We use medical records of the sampled participants to look at resource utilisation over the previous year, including inpatient and outpatient costs. The components of direct costs will include administrative costs, healthcare worker salaries, emergency medical services, pharmaceutical costs, diagnostic tests, physiotherapy, and others (Nordin et al., 2012). In addition, so-called “overhead” costs (which some researchers also call “indirect costs”) will be assessed; these include utilities and maintenance, rent, consumables, housekeeping services, and others. We will use a series of data collection forms (survey instruments) to capture the relevant information from participant medical records and from facility records. In all instances we will estimate economic costs of RHD care. Unlike the financial costs that accounts the actual expenditure of goods and services, the economic costs accounts for cost of all inputs, even if

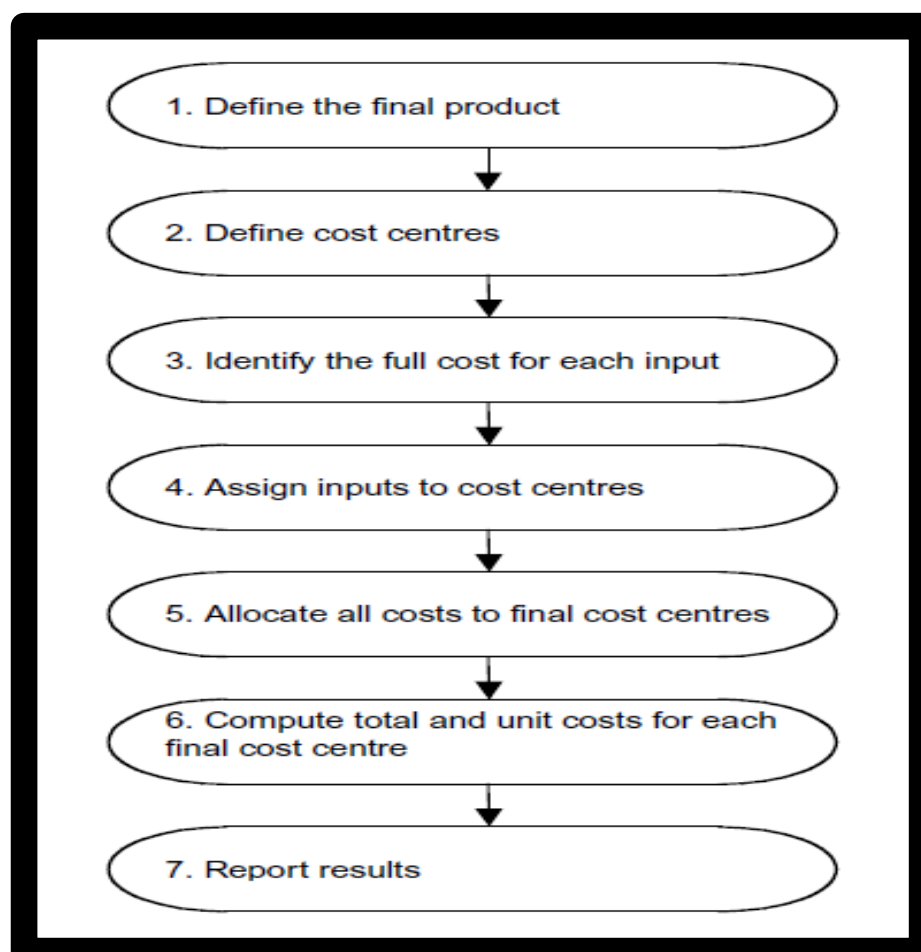
³ The study basis of the assumption for average inpatient cost of RHD care was; daily intramuscular penicillin plus 1 set of laboratory tests/electrocardiography/echocardiogram/chest x-ray.

these were provided for free including the value of the next best alternative foregone (i.e. opportunity cost) as a result of the use of resources (Conteh & Walker, 2004; Drummond et al., 2005). Estimating the opportunity costs of resources will allow us to account for worth of resources which are donated and/or voluntarily offered (i.e. money, materials or labour).

6.1 Estimating Overhead Costs Using the Step-Down Approach

The step-down costing method will be used to account for overhead costs of providing RHD care, including both recurrent and capital costs of the health facilities. While recurrent costs are resources with valuable lifetime of less than one year, capital costs are resources that have lifetime of more than one year (Hansen et al., 2010). In essence, the step-down approach will capture the cost of running GSH in order to provide RHD care directly (Drummond et al., 2005; Free et al., 2013). The step-down costing approach was explained in detail by Conteh and walker (2004), who summarised seven stages of step-down costing (Figure 1).

Figure 1: Summarised stages of step-down costing (Adapted and edited from Conteh and walker, 2004)



Conteh and walker (2004) also demonstrated that estimating costs within the health facility tier (i.e. indirect, intermediate and direct) should reflect flow of each cost centres resources. In order to capture all the costs incurred, we will divide various departments of GSH into final, intermediate and overhead cost centres.

Final refers to the departments that directly provide medical services to patients (Creese & Parker, 1994; Drummond et al., 2005) - in this study, outpatient and inpatient cost departments are the final cost/resource departments of this costing study.

Intermediate refers to the departments that render support services to the final cost/resource departments. These are drugs or/and diagnostic services which are often supported by pharmacy units or/and laboratory within the healthcare facility.

Overhead cost centers refers to general service support providing cost units that are crucial for the hospital to operate such as administration, maintenance and cleaning (buildings, laundry and linen) (Creese & Parker, 1994; Afriandi et al., 2010). The overhead cost centres render services to the entire hospital, so we will perform their cost first during step-down procedure costing. These will be followed by costing of intermediate departments, and the final cost departments will be estimated at the end. In summation, the cost of intermediate and overhead departments is allocated to the final cost department in a sequential manner.

The standard step-down methodology will be applied once the cost centres and departments have been identified (Hansen et al. 2000). In order to figure out the RHD cost in a stepwise manner, we will assign recurrent and capital costs to the various cost centres directly depending on their actual resource utilisation. A typical example will be the salary cost of administrative personnel, which will be assigned to the cost of administration centre, while the outpatient department salary cost of nurse depends on a proportion of time that the nurse spent in the outpatient department. Once all recurrent and capital costs have been assigned to various cost centers, the subsequent step will be assigning the overhead costs to intermediate and later to final cost centre.

The final step involves assigning the cost of running intermediate cost centres to the final centres. After completing the cost allocation to their respective final cost centres, we will divide the total cost of the outpatient department to the total number of outpatient visits in

order to obtain the unit cost per outpatient visit. Thus the total cost of RHD care from health care system perspective will be addition of the unit cost per outpatient visit (calculated using step-down approach) and average medical cost per person (calculated using the ingredients approach).

Data from the most recent financial records will be obtained. In a situation where financial records such as data on staff costs are absent, we will establish list of the employees who work in the department of concern and their salaries will be billed according to their salary rates. However, inventory list will be made available to capture capital goods (buildings, furniture and vehicles) if data is not available in this regard.

Capital costs will only be valued depending on their respective replacement costs. As demonstrated by Drummond et al., (2005) capital goods will be annualised using a discount rate of 3% in order to allow the depreciation and opportunity cost of goods (i.e. buildings, furniture, vehicles) purchase. The lifetime of these capital goods vary according to their categories. The estimated lifetime is generally 30 years for buildings, 10 years for furniture, and 5 years for vehicles (Creese & parker, 1994; Drummond et al., 2005). When performing the sensitivity analysis we will use 0%, 5% and 10% discount rate.

6.2 Estimating Direct Medical Costs Using the Ingredients Approach

Data on direct medical costs will be collected from medical records of the participants. We will review 100 medical records to determine service utilisation over the past year. Information on demographic characteristics, number of visits, attendance, diagnostics, and amount of medication dispensed to each participant will be collected from REMEDY study case report forms. Direct but non-participatory observation will be performed in order to establish the patient-provider interaction process (i.e. duration of patient-provider contact). Structured interview with one the staff involved in the RHD patients treatment will also be done in order to obtain information regarding various activities performed as well as the length of time spent on each activity. For each study participant, we will estimate the total direct medical cost of care as the sum of the cost of all the individual components of care described above. Each of these components will be costed by multiplying the quantity of resources consumed over the past year by the relevant price. In order to achieve this, we will

tabulate all RHD-related resources consumed over the past year for each patient as has already been recorded in their REMEDY case report forms. Prices will be obtained for all inpatient and outpatient goods and services from GSH separately. A brief overview of the costing methods and data requirements is provided under Appendix A.

7. Data Analysis

Raw data in the data collection instruments will be reviewed by a separate study member and verified and checked for errors. The study data will then be entered into Microsoft Excel (Microsoft Corporation, USA) for quality evaluation as well as performing analyses.

8. Sensitivity Analysis

While performing economic evaluations, number of assumptions or parameters are made and incorporated into the analysis. Consequently they cause uncertainties that may influence the results. One-way deterministic sensitivity analysis will be conducted in order to address such uncertainties, and to ensure the outcomes of this study are robust and comparable across different studies. Further, conducting sensitivity analysis will allow us to evaluate the uncertainty of our findings while allowing for generalizability to other research settings (Walker & Fox-Rushby, 2001). For this study, we will focus on the impact of major assumptions such as discount rates and utilisation rates of the clinical units (which we will collect by direct observation then apply uniformly to all participant data) evaluated one parameter at a time.

9. Ethical Considerations

This study will collect primary data on costs from the health facility and will conduct secondary analysis of medical records to obtain types and quantities of resources consumed in providing RHD care. The study entails minimal risk to patients and providers, and all participant data will be obtained in a de-identified format. First of all we will not record any personal/identifiable information of the patients. Second of all, this study is sub-analysis of REMEDY study that previously obtained ethical approval (HREC reference number 028/2006). However, ethical approval will be obtained from the Human Research Ethics Committee (HREC) of the University of Cape Town (UCT) prior to the beginning of the study.

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PART B: LITERATURE REVIEW

The aim of this section is to critically appraise the theoretical, methodological, and empirical literature focused on Rheumatic Heart Disease (RHD) and its economic burden on health systems. It will also identify the current gaps in the literature regarding the RHD burden in South Africa.

1. Theoretical Background of RHD

1. 1 Epidemiology of RHD

Heart valves assist the movement of blood through the chambers of the heart with each and every heartbeat. A disease that damages these heart valves, causing its failure to open and close normally, resulting in blood moving in the wrong direction, is called Rheumatic Heart Disease (RHD actions, 2017). It is also characterised as chronic inflammatory disease of the heart valves, and is primarily a disease of childhood and adulthood that results from recurrent incidences of acute rheumatic fever (ARF) (Moloi, et al. 2015). The main cause of ARF is untreated group A streptococcal (GAS) pharyngitis, causing a sore throat (Mayosi, et al. 2006; Beaton, et al. 2012; Zuhlke, et al. 2015). Streptococcal pharyngitis is an infection of the back of the throat including the tonsils with symptoms such as fever, sore throat and red tonsils (Ehrlich, et al. 2002; Carapetis, et al. 2005). However, RHD is a preventable disease if GAS pharyngitis is treated by means of benzathine penicillin that is an antibiotic which is useful for the treatment of a number of bacterial infections (Mayosi, et al. 2006; Watkins, 2015). Further occurrence and severity of the disease can be minimised through treating the patients with prophylactic penicillin in order to prevent additional cardiovascular damage (Godown, et al. 2015).

Despite its preventability, a large number of learners miss out on the opportunity to avert RHD by not presenting themselves to care before advanced heart failure occurs (Godown, et al. 2015; Zuhlke, et al. 2015). The main reason for patients not seeking healthcare can be the epidemiology of RHD in that it is usually dormant in its premature stages or during early childhood years (Zuhlke, et al. 2015). Most recent estimates indicate that there are 33 million people who suffer from RHD globally, with about 320,000 deaths in 2015 (Naghavi, et al. 2015). RHD sequelae include heart failure, as well as arrhythmias, stroke and infective endocarditis (Watkins, 2015). Most of these sequelae affect young school-going children and economically dynamic and childbearing adults (Araújo, et al. 2012). These conditions in turn lead to gradual disability, loss of quality of life and eventually premature death (Kumar & Tandon, 2013).

Unsurprisingly, high prevalence of RHD is mostly witnessed within nations from Africa, South Asia, and the Pacific Islands (Beaton, et al. 2012). Specifically, sub-Saharan Africa, South-central Asia, the Pacific and indigenous populations of Australia and New Zealand are worst affected (Mayosi, 2010; Seckeler & Hoke, 2011). These nations often struggle to tackle epidemic such as RHD as a result of inadequate resources. This is because RHD management requires policies that adequately recognise and devote resources towards its prevention and control (Mayosi, 2010; Moloi, et al. 2017). Failure to devote the required resources in order to tackle the RHD burden leads to severe conditions of the disease and it cripples the heart valves, causing heart failure and eventually premature death (Carapetis, et al. 2006; Zühlke, et al. 2015). Once it severely damages the heart valves, surgery is often required to repair or replace the valves of patients (Mayosi, et al. 2006). Surgery reduces the challenges and prolongs the life of the patients yet the cost is very high, and its burden on the healthcare sector resources is enormous (Carapetis, et al. 2006; Hewitson & Zilla, 2010).

1.2 RHD Disease Estimates

Low and middle income countries (LMICs) witnessed a decline in communicable disease, and thus mortality rates in children under-five, by more than a half between 1990 and 2015 after focusing on the implementation of millennium development goals (Curry, et al. 2017). However, studies suggest that further attention is required to reduce mortality and morbidity caused by neglect and non-communicable diseases (NCDs) (You, et al. 2015). One of the preventable and treatable forms of a disease that requires early detection, screening, diagnosis and treatment is RHD (Watkins, 2015; Zühlke, et al. 2015). However, RHD has been neglected for decades and it is a common cardiovascular disease (CVDs) in developing countries (Watkins, 2015; Moloi, et al. 2017). People living with RHD in developing countries account for about 80% of the disease, with the rest living in susceptible communities in developed countries (Robertson & Mayosi, 2008; Global Burden of Disease (GBD), 2013). Of this figure, more than 60% of school-aged patients drop out of school due to hindrances that RHD imposes, thus preventing them from realising their full potential (Yilgwan, et al. 2014).

RHD is one of the neglected NCDs, and its presence persists in LMICs (Moloi, et al. 2017). Lack of progress on addressing social determinants such as overcrowding, sanitation, nutrition, healthcare and awareness of the disease as a result of prolonged poverty in LMICs has been

an obstacle to fighting GAS, and thus addressing RHD (Curry, et al. 217). Studies have established that the prevalence of the disease is much higher in children of school-going age and young females of childbearing potential (Manji, et al. 2013).

The global RHD Registry (the REMEDY study) findings also stipulated that those affected by RHD are predominantly young, unemployed and female from backgrounds dominated by poverty and social injustice (Carapetis, 2007; Zuhlke, et al. 2015). These include poor access to primary healthcare as the main barrier to implementing primary and secondary preventions against rheumatic fever in most of the LMICs (Watkins, 2015). As a result, numerous patients present themselves late in the disease sequence of established RHD (Carapetis, et al. 2016). LMICs also face factors that arise from their health systems, such as a shortage of resources for health care, inadequate expertise of healthcare workers and low awareness of RHD within the communities causing inadequate (misdiagnosis or late diagnosis) treatment of RHD (Bronze, 1996; Mayosi, et al. 2006).

Currently, 2.4 million children aged between 5 and 14 out of 3.6 million affected globally reside in developing countries (Vos, et al. 2016). On the other hand, developed nations have witnessed major declines in ARF and RHD over the past decades (Mishra, 2007). The reason for the observed decline include improved living conditions, the presence of reliable primary health services (especially to treat sore throat to prevent ARF) and advances in the treatment of RHD, such as valve surgery (Brahmadathan, 2006; Mishra, 2007; Watkins, et al. 2016). Also, between 1.8 and 2.4 million African children suffer from RHD (Mayosi, et al. 2006; Vos, et al. 2016).

Africa is one of the highest affected continents, with the sub-Saharan Africa (SSA) region having the most estimated prevalence of RHD among school children (Mayosi, et al. 2006; Cilliers, 2015). SSA, which is home to only 10% of the world's population, is thought to account for 50% of children who suffer from RHD (Ntusi & Mayosi, 2009). The main socioeconomic determinants are poverty, overcrowding, low educational level, unemployment, malnutrition, and ill-equipped health systems (Longo-Mbenza, et al. 1998; Marijon, et al. 2012). As a result, countries such as the Congo, Mozambique and South Africa still experience high rates of RHD, with its attendant economic burdens (Mishra, 2007).

School-based studies in Mozambique indicated that the RHD prevalence in children is as high as 30 per 1000 (Marijon, et al. 2007) while incidence of new RHD cases among individuals over 14 years in Soweto, South Africa was 24 per 100,000 per year (Mayosi, 2010). Studies have found that 1 in 5 African children with RHD die by the age of 15, and 1 in 5 of them die by the age of 25 (Kimbally-Kaky, et al. 2002; Oli & Asmera, 2004). A systematic review published by Zühlke, et al. (2015), indicated that mortality caused by acute heart failure due to RHD was 25% at 60 days and 35% at 180 days. However among patients undergoing surgery, postoperative mortality was 2% at 30 days, and survival was 70% at 10 years, demonstrating that surgery, while expensive, can be a very effective intervention for RHD.

1.3 Economic Burden of RHD

The prevalence of RHD in LMICs amongst the children and young adults imply huge economic effects (Mayosi, 2010). Such effects hinder a country's growth through excessive direct and indirect healthcare costs at both the individual and national levels (Terrerri, et al. 2001; WHO, 2004; Hewitson & Zilla, 2010). The estimated economic and financial burden of RHD in low-income countries is believed to be a million times higher (\$56 billion) than the funds obtained from donors, and it requires an increase in public and private sector spending for effective prevention and control of the disease (Watkins, 2015; Watkins & Daskalakis, 2015). To mitigate these challenges, global research and development funding allocated \$1.7 million to RHD, that was only 0.1% of the global health fund for RHD in 2015 (Watkins & Daskalakis, 2015). However, lack of information regarding the costing and accurate clinical data have been said to be the main issues for funds to be distributed in low-income countries as per need (Mayosi, 2016; Shung-King, et al. 2016). In addition, lack of evidence for a more appealing plan, such as a return on investment to prevent deaths related to RHD, hindered the scaling up of expensive medical and surgical interventions in the region (Watkins & Daskalakis, 2015).

Surgical interventions impose high and irreversible costs on the health systems since severe RHD conditions can only be alleviated by surgery, if it is available at all (Gunter, Asmera & Parry, 2006; Watkins, et al. 2016). Still, the improved access to medical and surgical treatment for prevalent RHD cases also means high cost to the health systems for providing chronic care. High costs for RHD can also reinforce the "poverty trap" by incapacitating poor people with

high out-of-pocket payments (McIntyre, et al. 2006). On the other hand, the loss of young adults, which are the most productive and childbearing adult portion of the population, in turn undermines the national productivity of these countries (Araújo, Goulart & Meira, 2012). These factors can, in turn, hamper economic growth and development (Robertson & Mayosi, 2008). Furthermore, the management of the RHD burden could also pose enormous effects through exacerbating the existing inequalities in healthcare access and delivery for disadvantaged people in developing countries (Katzenellenbogen, et al. 2017).

If one takes a lesson from the available empirical evidence on CVDs, it is clear that the RHD burden affects health systems and hampered GDP by affecting households due to a need for out-of-pocket payments to access care. This is because CVDs, which are generally a low priority for public finance in many low-income countries, tend to result in catastrophic health expenditures at very high rates (Huffman, et al. 2011). This cost could also arise from patients paying for transportation and/or missing or losing jobs as a result of the disease. Yet we have no evidence for the economic impact of RHD on patients, with only one study to date (in Brazil) devoted to this topic (Terrerri, et al. 2001). In countries where the health system is ill equipped and under-financed, RHD possibly heighten the level of poverty (McIntyre, et al. 2006). This was intensified by the lack of access to evidence-based interventions in the regions (WHO, 2004; Watkins, 2015). Therefore, it is clear that LMICs need interventions and programmes to prevent and control RHD.

1.4 Interventions to prevent and treat RHD

RHD became rare in developed countries because of effective interventions that were put in place. Evidence indicates that countries such as Australia, New Zealand and the USA have seen huge declines in disease incidence, largely by using penicillin for primary prevention (Carapetic, 2007). Improved living conditions and better hygiene reduced overcrowding while malnutrition, also contributed towards the decline of the disease (Carapetic, 2007). The consequence of this decline has seen parallel Reduction in RHD related research and left the LMICs to tackle the burden on their own. Therefore, LMICs need to draw a lesson from the developed world regarding potential preventative and treatment measures to fight RHD. *Table 1* illustrates the interventions and preventative measures recommended by the World Health Organization (WHO) (WHO, 2004).

Table 1: Potential Preventive Measures of ARF/RHD

Interventions/preventative measures of ARF/RHD	Description	Potential outcomes of the intervention/preventative measures of ARF/RHD
Primordial prevention	Having improved environmental conditions and access to resources that improve living conditions (i.e. clean housing, hygiene, nutrition, sanitation and overcrowding) as well as other social determinants of health (i.e. employment, education and infrastructure)	Reduces risk factors for Group A streptococcal (GAS) infections (strep throat)
Primary prevention	Effective screening using echocardiography, diagnosis and treatment of strep throat at the primary level of care	Prevents the initial attack of acute rheumatic fever (ARF)
Secondary prevention	Administering people with a history of rheumatic fever with antibiotics (specifically preventing with benzathine penicillin) to avoid GAS infection	Minimizes subsequent ARF recurrence and progression of ARF to RHD
Tertiary prevention	Providing advanced medical and surgical care such as heart valve replacement/surgery and medications	Manage cardiac heart failure, prevent stroke, reduces chances of premature death

From the potential ARF/RHD prevention measures illustrated above, secondary prevention programmes have proved to be cost-effective and practical even in the poorest countries

(Carapetic, 2007; Irlam, et al. 2013). Available empirical literature also underscores the fact that the secondary prevention programmes are mostly cost-effective and efficient compared to the notions of primary prevention programmes (Michaud, et al. 1999; Manji, et al. 2013). This is because primary prevention is believed to be effective in well-resourced settings and less practical in LMICs where disease rates are high and the health system is ill-equipped (McDonald, et al. 2005). Several studies also highlighted the importance of reducing hospitalisation and surgery by utilising antibiotics (secondary prevention) while advocating for integration of existing primary healthcare systems in order to eliminate the cost burden of RHD (Nordet, et al. 2008; Watkins, et al. 2015).

1.5 Country Profile - South Africa

1.5.1 Demographic and Economic Features of South Africa

According to the World Bank estimates of world economies, South Africa is a middle-income country with an abundant supply of natural resources (World Bank, 2014). The country's population estimate for 2015 was 56 million with 12 million of the population living in extreme poverty (Statistics SA, 2014). High levels of poverty imply a high burden of healthcare expenditure for the government, with the National Department of Health (NDoH) holding general accountability (Koch, 2011; Ataguba, 2015). In addition, the prevalence of unemployment, poverty and inequality in South Africa has been accelerated in recent years by lowered economic growth, slowing to 0.4% in 2016 (National Treasury SA, 2017). While the high unemployment rate persists, due to the negative effects of slow economic growth rate, the government continues to focus on controlling inflation (South African Reserve Bank, 2017); yet, the country continues to face structural challenges (i.e., shortage of skills, frequent stoppages of work because of strikes and a decrease in global competitiveness) which, in turn, constrain economic growth (Van Broekhuizen, 2016). As a result, the current government faces increased pressure from the listed challenges, while the economic outlook is also expected to remain slow (Van Broekhuizen, 2016; National Treasury SA, 2017).

1.5.2 Health System Context and Structure of South Africa

South Africa's health system comprises of a large and fast growing public sector, but smaller private sector, and non-government organisations (NGOs) (Jobson, 2015). The country has

4200 public sector facilities with 13, 718 individuals on average receiving treatments from each clinic (Bekker, et al. 2014). The facilities host 2.5 visits from people on average each year with bed occupancy rate in hospitals being between 66% and 77% (Jobson, 2015). The public sector utilises 11% of the total government budget which is more than the 5% recommended by WHO (McIntyre & Thiede, 2006). South Africa has poor health outcomes despite this high government expenditure, replicating greater inequality within the healthcare compared to other middle-income countries (Bekker, et al. 2014; Ataguba, 2016). It is also believed that the quality of the public sector healthcare provision is hindered by a shortage of crucial medical personnel (International Council of Nurses, 2006; Wyber, et al. 2014).

1.5.3 Healthcare Provision and Financing in South Africa

Besides the challenge of heavy burdens from NCDs and communicable diseases, the healthcare provision and financing in South Africa is controversial and inequitable, while about 12 million people live in extreme poverty (Statistics SA, 2014). While formally employed and those which are well-off obtain healthcare from private and public sector, poor is limited to the inadequate and underfunded public sector healthcare (McIntyre & Thiede, 2006). Even though the government has embarked on a National Health Insurance scheme, it has a long way to go before it provides equitable healthcare access (McIntyre, et al. 2014). Currently, about 80% of the population depends entirely on the public sector for all health services, while heavily subsidised private healthcare and inpatient care is available for merely 16% of the population (Ataguba, et al. 2011). In the meantime, the public health system carries an inevitable financial burden, and hence inefficient and inadequate care has been provided for the majority of the population, specifically the poor who are exempt from service payments or user fees when seeking care in the public sector (Ataguba & McIntyre, 2012). In addition, the poor also encounters out-of-pocket non-medical cost payments such as transport and food when confronted by largely preventable but neglected diseases (Douglass & Modie, 2016). In South Africa, out-of-pocket healthcare payments contribute 13.78% of overall health sector expenditure while government contributes about 44%, and medical schemes covers 42% (Ataguba, 2012; Nicolson, 2015). This is relatively high for a middle-income country such as South Africa when compared to 0.5% in low-income countries such as Sudan and Djibouti, signifying that out-of-pocket payments relative to government expenditure deserve attention in South Africa (McIntyre and Kutzin, 2011).

1.6 Epidemiology of RHD in South Africa

In 2010, the incidence of new RHD cases among individuals over 14 years in Soweto, Gauteng was 24 per 100,000 per year (Mayosi, 2010). A systematic review published by Zühlke, et al. (2015), indicated that mortality caused by acute heart failure due to RHD was 25% at 60 days and 35% at 180 days. However, the same study reported that among patients undergoing surgery, postoperative mortality was 2% at 30 days, and survival was 70% at 10 years, demonstrating that surgery, while expensive, can be a very effective intervention for RHD. On the other hand, Cillers (2014) working in Soweto reported a decline in the number of children with ARF and RHD visiting to Chris Hani Baragwanath Hospital in Soweto, South Africa from 1993–2010. Yet, a echocardiographic screening study of school-children in Cape Town revealed a prevalence of hidden RHD of 20-30 per 1000, as well as changing patterns of the disease (Engel, et al. 2015). Shung-King, et al. (2016) revealed that 50% of these cases alter to normal if followed up for 5 years. South African Cardiovascular diseases (CVDs) guidelines recommend for areas, where there is a RHD epidemic, that all cases of sore throat in children between 3 and 15 years of age should be treated as streptococcal infection (Mayosi, et al. 2010).

The high burden of RHD related heart failure and mortality, as mentioned in a study by Zühlke, et al. (2015), and demonstrated in Soweto recently, have declined in South Africa since 1997 (Mayosi, 2016). These observations highlight that, while the RHD condition persists in South Africa, health outcomes are improving, undoubtedly because of the ‘Mandela dividend’ associated with socioeconomic improvement, and enhanced access to primary health care (including surgical facilities) (Zühlke, et al. 2015). Still, improved access to medical and surgical treatment for prevalent cases also means high costs to the health system for providing chronic care.

This costly disease was made a notifiable condition in October 2005 during the 1st Pan-African conference on ARF and RHD hosted by the National Department of Health (NDoH) of South Africa (Mayosi, 2016). During this conference, a clarion call to African governments and their ministries of health was made to adopt programmes to abolish ARF and control RHD by increasing awareness, surveillance, advocacy, and prevention (ASAP) was adopted (Engel, 2012; Mayosi, 2016). The adoption of these programmes was followed by the Addis Ababa

Communiqué in June 2015, when African heads of states endorsed seven action plans to address the obstacles to RHD control that were acknowledged in the REMEDY study (Zühlke, et al. 2015; Watkins, et al. 2016). It is believed that South Africa has the required conditions to successfully eradicate ARF and RHD (Mayosi, 2016). The NDoH launched the National Rheumatic Fever Week, labelling ARF amongst notifiable conditions in an effort to improve access to primary healthcare (NDoH, 1997; Mayosi, et al. 2006). However, healthcare practitioners also need to be trained in order to notify ARF cases, utilise the electronic registry to capture the new patients with sore throat and treat them with penicillin as the South African ARF/RHD guidelines (South African National Department of Health, 1997; Mayosi, 2016). RHD community has relatively small amount of advocates, clinicians and researchers compared to the enormous group of stakeholders in large disease communities (i.e., TB)(Wyber et al., 2014). However, investigating the impact of these conditions that are believed to hasten the demise of ARF/RHD in South Africa is crucial.

2. Methods for Estimating Healthcare Costs

2.1 Economic Evaluation in Healthcare

Consumer economics assumes that consumers make choices intended at maximising their level of satisfaction, and that optimal choices are made once the consumer has been provided with full information (Cunningham, 2000; Drummond, et al. 2005). However, persons who present themselves for health care are often unable or reluctant to provide the required information that will enable them to exercise their choice to access health care (Ataguba, 2012). This consumer side of failure is further complicated by the fact that the person supplying the needed information to the prospective patient is the very same person supplying treatment which does not occur in other fields, but in the healthcare sector (Cunningham, 2000; Tenkorang, 2016). Because of this, allocating healthcare resources in an efficient and equitable manner has always been a controversial matter (McIntyre & Kutzin, 2011; Ataguba, 2012). As a result, economic evaluation in healthcare has become more important in recent years, and now it is an accepted tool for the appraisal of healthcare programmes (i.e. health financing policies) (Chisholm & Evans, 2007).

Full economic evaluation includes four types of approaches: cost-effectiveness analysis (CEA), cost-utility analysis (CUA), cost-benefit analysis (CBA) and cost minimisation analysis (CMA) (Cunningham, 2000; Drummond, et al. 2005). Economic evaluation is often defined as a systematic approach, which is utilised to compare and contrast two or more interventions on a basis of costs and outcomes (Drummond, et al. 2005). In particular, CEA compares and contrasts alternative interventions versus primary objectives of the programmes in order to estimate the level of reduction in morbidity and/or life years saved in natural units (Frick, 2007). CUA compares similar interventions as CEA but utilises more broad outcomes such as quality-adjusted life years (QALYs) and disability-adjusted life years (DALYs) measured directly from patients (Drummond, et al. 2005; Frick, 2007). It is a preferred approach when evaluations comprise numerous objectives within the programmes, and both quality and quantity of life are vital outcomes (McCabe, 2009). CBA compares interventions using broad monetary outcomes (i.e. Rands) and differs from CUA because it values health outcomes depending on subjective judgements with techniques such as willingness to pay (Drummond, et al. 2005; McCabe, 2009).

Another economic evaluation approach that only deals with the initial (first) section of an economic evaluation is called cost analysis (Creese & Parker, 1994; Cunningham, 2000). The cost analysis approach is often used in disease-specific studies to assess the cost of providing healthcare. On the other hand, the cost analysis approach does not assess outcomes, so it is considered as a partial economic analysis approach (Creese & Parker, 1994; Drummond, et al. 2005). When there are no data on interventions for a specific disease, researchers and policymakers can use cost analysis, particularly in areas that have not been explored before. A cost analysis of RHD in South Africa, for instance, may spur greater interest on the part of government in developing interventions, and the costs can also serve as inputs for future full economic evaluations.

2.2 Cost Analysis in Healthcare

When performing cost analysis for disease-specific cost of care, cost items can be valued using two approaches: ingredients (bottom-up) and step-down (Flessa, et al. 2011). Determining which approach to use for any chosen study is a key decision in costing which fundamentally affects the cost and the resources required to conduct the study (Cunnam, et al. 2016). In

simple terms, the ingredients costing approach is usually measured through multiplying resources used (input) by their prospective cost/price of the input (Rupert, et al. 2016). In order to estimate the unit costs, this approach uses detailed action and input utilisation data from records on detailed activities and observed resource usage from the level of the service provider (Batura, et al. 2014). The ingredients approach captures resource utilisation at individual or patient service level (Muennig & Khan, 2002; Mogyorosy & Smith, 2005). Its resource allocation is often based upon the authentic contribution of explicit resources, particularly indirect costs, such as administrative related costs, and others that support patient care and represent a significant proportion of the total cost of care (Chapko, et al. 2009). It also uses the aggregate service level of resource utilisation data in order to classify the type of resources utilised by patients, as well as to estimate or calculate the cost of specific services rendered (Mogyorosy & Smith; Batura, et al. 2014).

The step-down approach requires the analyst to take the overall expenditures of the inputs/ingredients at a central level (Conteh and Walker, 2004; Cunnama, et al. 2016). The allocation of costs in step-down costing are dealt with by using methods based on the allocation factors in order to establish unit cost of the service provider (Muennig & Khan, 2002; Flessa, et al. 2011).

Various studies comparing the ingredients costing approach and the step-down approach suggest that the ingredients approach is likely to be more precise because it captures resources more comprehensively and can be more accurate when compared to the step-down approach (Hendriks, et al. 2014; Cunnama, et al. 2016). This is because the ingredients approach in principle is reliable and flexible, containing evenly detailed comprehensive data while its counterpart could contain data which may differ depending on the area of study (Wordsworth, et al. 2005; Cunnama, et al. 2016). The ingredients costing approach simply requires data which can be easy to access, and it is more suitable for non-homogeneous (intensive care) services compared to the step-down costing approach that assumes equal distribution of resource utilisation between patients (Negrini, et al. 2004; Hendriks, et al. 2014). In addition, the ingredients costing approach enjoys resource utilisation measurement method flexibility when recording data, unlike the step-down costing approach which is dependent only on financial accounts data, as illustrated in Table 2 (Wordsworth, 2005).

Table 2: Measurement approaches (adapted from Mogyorosy & Smith (2005) and modified)

		Costing approach in Relation to time	
		Retrospective	Prospective
Data recording approach	Ingredient s costing	Uses medical records, cost accounting, billing, surveys as well as questionnaires	Uses medical records, cost accounting, billing, surveys as well as questionnaires
	Step-down costing	Uses hospital information system (including accounting, accounts, vehicle register, etc.)	In practice, it is not possible to obtain data easily. Unless assumptions are drawn on previously available data.

As indicated in Table 2, because the step-down approach depends on financial accounts and other databases, it is retrospective in practice, while a bottom-up approach can be either retrospective or prospective. Prospective data collection can be more flexible and tailored towards the objectives of the study, but time consuming, expensive to commence, and it is specific to settings (Merx, et al. 2003; Simoens, 2009). The reason behind the downside of the ingredients costing approach could possibly be that it assesses cost of individual services within complex integrated healthcare systems, and that may account for its more limited acceptance (Chapko. et al. 2009; Cunnama, et al. 2016).

On the other hand, the step-down costing can be less costly and faster compared to the ingredients costing approach (Mogyorosy & Smith, 2005; Cunnama, et al. 2016). This is based on the fact that the step-down costing captures the total cost in a central/departmental level, and then dividing the total cost of the cost centres with the number of patients receiving treatment or the number of inpatient days (Waters & Hussey, 2004; Negrini, 2004; Chapko, et al. 2009). As a result, the step-down costing cannot be used to measure minimal alterations in resource consumption, for instance, inside hospitals, because the step-down costing

cannot differentiate between individual patient consumptions (Elliott & Payne, 2005; Simoes, 2009). In turn, several studies where costing involved complex hospital services and partly where it lacks detailed available data regarding resource utilisation, the step-down costing approach could be the only feasible option (Adam, Evans & Murray, 2003). However, one of weaknesses of step-down costing is its being less accurate, and hence it captures less detailed retrospective data, as well as resource allocation that can be more or less subjective (Mogyorosy & Smith, 2005; Cunnama, et al. 2016). Furthermore, the aforementioned could be worsened by the fact that this approach may or may not contain the correct detailed information regarding the quantity of services rendered, nor the relative resources consumed for specific product/service in a reliable and sufficient manner (Muennig, 2002; Elliott & Payne, 2005). Therefore, a step-down approach could overestimate a unit cost of a service if patients acquire more services than an anticipated quantity or it could underestimate if fewer services are rendered than reported (Mogyorosy & Smith, 2005; Cunnama, et al. 2016).

In addition, a study by Wordsworth, et al. (2005) that compared both step-down and ingredients costing approaches using two different diseases in France, Greece and Hungary established that the estimated costs and the actual cost differences depend on the costing method used. Other authors agreed with these findings, further stipulating that the ingredients costing approach is the most cost effective driver, as it is the only approach which clears up the real causes of cost differentials (Mogyorosy & Smith, 2005; Chapko, et al. 2009; Cunnama, et al. 2016), in addition to indicating the more practical weakness of the step-down costing side compared to its ingredient costing counterpart. However, the ultimate and practical accuracy of costing to estimate health systems costs/expenditures can best be common by comparing it to costing gold standard rules (Drummond 2005; Chapko, et al. 2009). Unfortunately, gold standard rules for costing approaches do not exist as a result of controversies that would emerge as to whether ingredients, step-down, or utilisation of the mixed approach yields the best projection of 'true costs' (Mogyorosy & Smith, 2005; Mercier & Naro, 2014). In the absence of gold standard rules, researchers have different practical views about ingredients and step-down costing approaches (Chapko, et al. 2009; Cunnama et al., 2016). Further detailed explanation regarding the practical differences to some extent of researcher's agreement regarding the two approaches is illustrated in *Table 3*.

Table 3: Major practical methodological differences between ingredients and step-down approach

Aspects of methodological differences	Ingredients approach	Step-down approach
Cost allocation	Cost allocation, and shared cost distribution often more standardised i.e., greater consistency in between study/costing centres/sites	Cost allocation of overhead costs often depends on the existing cost bookkeeping system as well as the distribution of shared costs. This could be unclear, not transparent and eventually differ by centres/sites
Separation between unit price and resource Utilisation	It permits separate recording as well as reporting of prices and resources. Prevailing higher transparency	Not constantly possible to separate. more difficult in hospital related studies
Data availability and reliability (unit prices and resource utilisation)	Easy to attain well detailed data/information in standard format from any study sites/centres. It requires dedicated personnel since it requires intense time	Difficult to attain detailed and well-structured data/information. It is even more difficult in LMICs, where cost bookkeeping is unsophisticated
Data extensiveness	Possible to be consistently detailed in different sites	It differs depending on sites/settings
Detection of treatment of disease policies, patterns/resource utilisation	Possible to detect/identify the differences	Challenging to identify. Not possible at times

One of the few studies that compared and contrasted methodological aspects described the step-down approach as an approach that smooths out cost variances “over time and in between patients” because it applies similar weights to identical products/services regardless of individual/patient, time or setting (Chapko, et al. 2009). On the other hand, the ingredients approach was described as an approach that puts emphasis on time and individual/patient

differences because it constructs costs from resource utilisation which can fluctuate 'over time and in between patients' (Conteh and Walker, 2004; Flessa, et al. 2011).

Further studies that compared costing approaches using the national data in the United States of America highlighted that the strength of the ingredients approach was better able to capture site-level differences, whereas the step-down approach was better able to capture national long-run average costs (Chapko, et al. 2009; Flessa, et al. 2011). Currently, available costing literature also agrees with the fact that both approaches provide deviating cost estimates (Cunnama, et al. 2016). Studies focusing on questions and implications, such as when and under what conditions are these approaches complementary, and when and for what commitments should either perspective approach be used, are vital to conceptualise the reasoning behind the existence of the differences between the approaches (Flessa, et al. 2011). Thus, acknowledging these differences can assist researchers; however, it requires them to be explicit about their intended use of prospective approaches and potential measurement errors of their estimates that could arise as a result of single cost data source (Hendriks, et al. 2014).

In practice, disease-specific studies have been utilising the mixed approach in their methodologies, somewhat driven by low availability of unit prices, detailed input and resource utilisation data (Drummond 2005; Chapko, et al. 2009). Several published studies, including Britain's National Health Service (NHS) costing guidelines, the Veterans Affairs (VA) consensus guidelines in the USA, as well as a study of incremental cost of new technologies in South Africa, have applied the mixed costing approach (Swindle, et al. 1999; Mogyorosy & Smith, 2005; Cunnama, et al. 2016). The main advantage of implementing a mixed approach could be avoiding some of the weaknesses of both the step-down and ingredients costing approaches (Shepard, et al. 2000; Hendriks, et al., 2014; Cunnama, et al. 2016). This is because using a mixed approach can be cheaper than an individual ingredients approach, and it can be more accurate than employing merely a step-down approach, hence it reflects in variations of resource utilisations as required by several costing studies (Chapko, 2009; Hendriks, et al. 2014).

The importance of implementing a mixed costing approach allows researchers to prioritise cost estimation in relation to their study objectives, and determine where or on what to base

the direct cost estimation on (i.e. ingredients approach), and when to use the financial accounts based databases (i.e. step-down approach) (Mogyorosy & Smith, 2005; Hendriks, et al. 2014). This approach further assists cost of illness, cost analysis, and cost-effectiveness studies to cope with issues arising from missing data and/or gathering information/ collecting data which was not conventionally collected (Mogyorosy & Smith, 2005; Sarowar, et al. 2010), indicating that the mixed approach is routinely applied in cost studies to obtain estimates such as incremental costs that are used in cost analysis during economic evaluations. For instance, the study by Hendricks, et al. (2014) suggested that the staff costs be estimated using ingredients costing, while the building space and vehicles may be assessed using the step-down methodology. Recent literature that advocates for the usage of a mixed approach also calls for researchers to be clear about their objective when evaluating, mixing or assuming costing for different resource usages (Hendricks, et al. 2014; Cunnama, et al. 2016).

2.3 Evaluation of Costs

Cost evaluation depends on who utilises the resources and who incurs the cost. Cost solely borne by patients and households is called cost from a patient perspective (Weinstein, et al. (1996), while the provider perspective costs include solely of those costs that healthcare providers incur in a form of intervention (Creese & Parker, 1994). On the other hand, a societal perspective comprises both provider and patient cost perspectives, and it is the most comprehensive perspective of economic evaluations because it takes into consideration health benefits and profitability of any given intervention (Jonsson, 2009). Costs of an intervention borne from the provider's perspective in healthcare scenarios include cost estimations of medications, overheads and laboratory tests, but cost incurred by patients or households are not included (Creese & Parker, 1994). Such cost evaluations are vital when determining the practicality of piloting expansion and/or a change of interventions or even scaling up the existing one (Hongoro, 2017).

Costs are made up of two different components, namely amount/quantity of resources utilised and their respective unit prices (Drummond, et al. 2005). Various elements of cost analysis are separately evaluated when estimating costs incurred. Financial costs refer to the actual monetary expenditure on inputs utilised in order to provide goods or services, while the economic costs refer to the best alternative forgone or the opportunity cost of the

resources utilised (Conteh & Walker, 2004). Evaluating the opportunity cost of resources aid to account for the worth of resources which are donated and/or voluntarily provided. According to Drummond, et al. (2005), financial and economic costs are further categorised into capital or recurrent, depending on their estimated life years and value. Resources that are primarily a creation of fixed assets with a usable time frame of more than a year and value of greater than US\$100 (i.e. buildings, furniture, vehicles) are capital costs (Hansen, et al. 2010). Recurrent costs refer mainly to resources which are regularly purchased, and their estimated life expectancy is less than a year (i.e. salaries of personnel, electricity, medications) (Creese & Parker, 1994, Hansen, et al. 2010).

The building costs are usually estimated by using square metre of spaces utilised and multiplied by the replacement value of buildings per square metre. The estimated financial costs of capital items are depreciated using a straight-line rate, while the economic costs are annualised using a discount factor of 3%, as advised by the World Health Organization (WHO) (Drummond, et al. 2005). The advised factor allows for depreciation and it accommodates the opportunity cost of purchasing the capital items (Hansen, et al. 2010). The estimated lifetime of 30 years for buildings and 10 years for equipment and furniture are used in costing research. Overhead costs for both outpatient and inpatient care are often estimated using patient day equivalent (PDE) (Clearly, 2007). The PDE is estimated as:

$$PDE_{\text{outpatients}} = (\text{annual inpatient days}) \times \frac{1}{\text{weighting factor}} + (\text{annual outpatient visits})$$

$$PDE_{\text{inpatients}} = (\text{annual inpatient days}) + (\text{annual outpatient visits} \times \text{weighting factor})$$

The weighting factor is the average ratio of overhead costs per outpatient visit to the cost per inpatient day, whereas the standard assumption in South Africa is that an outpatient visits costs one-third ($\frac{1}{3} = 0.33$) of an inpatient day cost (Clearly, 2007). The outpatient visits and inpatient days PDE will be estimated as;

$$PDE_{\text{outpatients}} = (\text{annual inpatient days} \times 3) + (\text{annual outpatient visits})$$

$$PDE_{\text{inpatients}} = (\text{annual inpatient days}) + (\text{annual outpatient visits} \times 0.33)$$

Therefore, overhead costs of outpatient visit and inpatient day will be calculated as:

$$\text{Overhead cost per outpatient visit} = \frac{\text{annual overhead expenditure}}{\text{PDE}_{\text{outpatients}}}$$

$$\text{Overhead cost per inpatient day} = \frac{\text{annual overhead expenditure}}{\text{PDE}_{\text{inpatients}}}$$

2.4 Discounting and Annuity

Discounting is used to determine the present value of resources that is to be received in the future (Walker & Kumaranayake, 2002). Researchers often utilise it to adjust future outcomes of resources and their respective present-time value. This is important given the fact that the values of resources vary depending on when they are being used and yield benefits. Drummond, et al. (2005) stated that individuals choose to obtain benefits in the present and pay in the future. Thus, to account for this time preference, discounting is utilised to adjust for future costs and future outcomes. Usually, such resources fall into a capital cost category and are purchased once off (Hansen, et al. 2010). A discount rate of 3% & 5% are often used by researchers to ensure the robustness of the outcomes (Vassal, et al. 2017). On the other hand, annuity is used by researchers to allocate the economic cost of capital items for a given year. It is performed by taking into account depreciation and the interest from the investment foregone in order to purchase these items (Walker & Kumaranayake, 2002). The lifetime of the capital items vary accordingly, mostly 30 years is used for buildings, 10 years for furniture, and 5 years for vehicles (Creese & Parker, 1994). However, discounting and annuity rates differ depending on the settings and the assumptions utilised particularly in disease-specific programs and preventions. And there are available costing tools with a detailed list of ingredients and some collection of overhead costs at the service level to guide researchers when estimating disease-specific costs in LMICs (UNAIDS, 2011; WHO, 2016).

2.5 Review of Methods Used to Estimate Cost of Disease Specific Care: Health Systems Perspective

In general, inpatient costs are neglected for non-communicable disease (NCDs), predominantly CVDs. Estimating the costs for CVDs include economic measures to assess the impact of disease treatment on healthcare costs (Radensky, et al. 2001; Saxena, et al. 2006; Riley, et al., 2016). However, most of the CVDs literature to date has focused on outpatient primary care/prevention costs as a rule of thumb to estimate cost estimations (Adam & Evans,

2006; Toulany, et al. 2015), whereas the ratio of inpatient cost of care to outpatient cost of care vary according to hospital size and occupancy rate (i.e. rules of thumb do not hold accurate cost estimation) (Kalisvaart & Hergenroeder, 2007; Toulany, et al. 2015). Few systems cover resource usage in general, while a broad system focus on major drivers of total costs, such as inpatient hospitalisation care (Adam & Evans, 2006; Hansen, et al. 2017). Studies, such as Radensky, et al. (2001) and Hansen, et al. (2017) imposed different approaches to categorise costs in order to estimate resource utilisation of cardiovascular events. The former derived costs from hospital bills, while the latter obtained the estimation of provider costs from the payer allowances, as well as various cost reports and financial analyses. This makes comparison between results difficult and incomparable among different trials and analyses (Radensky, et al. 2001; Hansen, et al. 2017).

On the other hand, several studies highlighted that the length of hospital stay (inpatient care) is the largest portion and a determinant of total cost in healthcare costing (Macario, et al. 1995; Radensky, et al. 2001; Saxena, et al. 2006; Toulany, et al. 2015). A study that investigated hospital costs of surgical procedures estimated total cost through dividing it into operating departments, such as operating room, ward, surgery admission unit, laboratory, pharmacy and miscellaneous (Macario, et al. 1995). The authors further subdivided the departments to accommodate unit costs of all events, using patient-specific data. As such, operating costs comprised the equipment, labour and supplies utilised once the patient had been admitted for inpatient care, while miscellaneous included the ambulatory services, therapy and dietary services (Macario, et al. 1995).

Radensky, et al. (2001) also assessed costing methods for inpatient care costs of major CVD events. The study established that average inpatient hospitalisation costs can be calculated using patient level data, given national estimates. For instance, the estimation of admission costs for an individual event was recommended to be calculated from the average hospital costs of all charges for patients, followed by converting the charges per admission to estimate the costs per admission and utilising the national median cost-to-charge ratio. While the cost of physician(s) was suggested to be included only for patients who went through surgery, the total cost-to-charge should be obtained from the sum of individual cost-to-charge ratio of operating and capital costs. The findings proved that total direct cost of hospital stay and discharges to institutions in stroke patients were determined by medical complications

(Radensky, et al. 2001; Saxena, et al. 2006). In addition, empirical literature indicates that low-and-middle income countries face additional alarming issues, such as health systems being generally ill-equipped to manage chronic disease, as well as to measure the cost of hospitalisation care (Brouwer, et al. 2015; Hansen, et al. 2017).

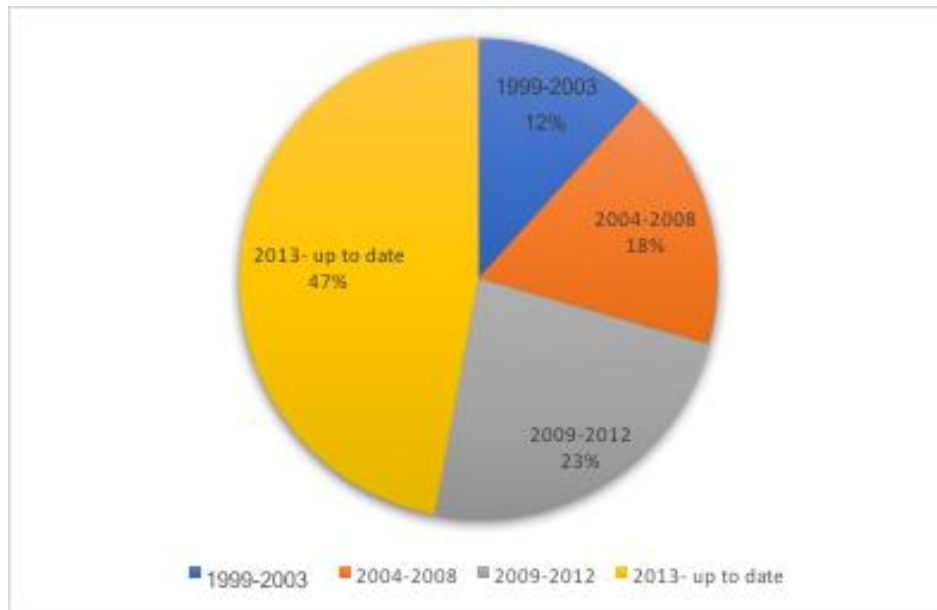
3. Review of Studies on the Cost of RHD to Health Systems

3.1 Search Strategy

A published papers search was conducted according to the databases content with the main focus of containing economics field literature. The search included the following databases: PubMed (NCBI), Scopus, EBSCOhost (CINAHAL), EBSCOhost (EconLit), EBSCOhost (Africa wide information), and Central Cochrane. Search terms specifically adapted to each database using 1) terms related to ARF/RHD and some risk conditions; 2) terms related to health systems and healthcare provider; and 3) terms representing cost. The full systematic search report and the search strategy process can be found in Appendix D. Out of 481 studies, 29 studies met the inclusion criteria of studies of the cost of RHD from the health system perspective, given the restricted disease condition of interest to ARF and RHD.

The number of published articles for ARF/RHD in LMICs is unsurprisingly rare. Most of the studies on the burden/cost/cost-effectiveness of ARF/RHD are conducted in upper middle and high income countries, with very little studies attempted in low-income countries. Regardless of whether the studies are cost related or not, the sample studies are mainly from Asia and the United States, dominated by studies from India. Figure 2 provides the year and number of articles published from 1999 to date. The year 2013 saw the highest number of articles discussing ARF/RHD burden-related articles which was not surprising, given the increase of research on cardiovascular studies in general, as confirmed by Elizabeth, et al. 2015 study.

Figure 2: Number of published articles related to burden of ARF/RHD from 1997 up to date



3.2 Cost Estimation and Management of ARF/RHD Burden

The search review identified 7 studies that focused on the treatment and management of RHD and post-RHD conditions. The cost of pre- and post-RHD complications also includes treatment of sore throat, ischemic heart disease, stroke, heart failure, among others. Treatment or the care of RHD typically consists of screening, diagnostic procedures, surgical, and other advanced treatments, and post-surgical and long-term outpatient care (i.e. medications and check-ups). The highest inpatient costs were associated with long hospital stay days that are related to more severe conditions of RHD. The costs ranged from \$49 for part of inpatient treatment to \$128,000 for inpatient care, including surgery and hospital stay per-patient. The mean inpatient cost of ARF/RHD varied widely, depending on the geographical settings, the actual resources utilised and the mean length of hospital stay. However, most of these articles provided estimated cost, treating ARF/RHD without distinguishing neither the severity of the disease nor do they clearly establish a breakdown of outpatient and inpatient costs.

It was also evidenced that RHD is a declining disease in developed world that affects the elderly as hidden during its early stages, and that it is regularly associated with supplementary chronic diseases (Marijon, et al. 2012). As a result, developed countries face more per-patient cost of RHD, given that they have higher prices and greater utilisation of advanced medical

care than their developing counterparts (Marijon, et al. 2012). The difference in prices and utilisation highlights as the cost of RHD treatment varies from region to region. For example, per-patient cost of care in the United States of America in 2002 was about \$6000 (Ehrlich, et al. 2002), while per-patient cost in China in 2012 was about \$4700 (Wang, et al. 2015). A study from Havana, Cuba also indicated that the cost of severe RHD care in the 1990s was about \$6300 (Watkins, et al. 2015), while the cost burden per-patient in South Africa for merely inpatient care in 2010 was \$2900 (about R39, 000) (Irlam, et al. 2013).

A hospital-based study of 453 RHD attributed ischemic stroke patients by Hashmi, et al. (2013) at one of Pakistan's largest tertiary care hospitals found that the average cost of care per-patient was 70 714 rupees (US\$1179). The average cost of care per-patient was confirmed to be much higher than the per capita income of US\$672 in Pakistan (Hashmi, et al. 2013). Another study from New Zealand further highlighted that hospital admissions and related yearly costs to the government were more expensive in the age group 5 to 14 years (Richard, et al. 2012). From the costs incurred, non-surgical expenses were the highest expenses that accounted for well over half of the total provider cost (Richard, et al. 2012). However, hospital admissions for RHD are more common among Brazilian patients in the age group 20 to 60 years. (Guilherme, et al. 2012). Brazil has also witnessed a low frequency of RHD patients towards hospital admissions because the recent disease burden belonged to a younger age group (Guilherme, et al. 2012). With a mean follow-up time of 3.9 years (age range 1–10 years), patients had a total of 1657 medical consultations, 22 hospital admissions and 4 admissions to an intensive care unit (Guilherme, et al. 2012).

At the same time, the economic impact of RHD is felt more by LMICs health systems because these countries encounter much higher numbers of RHD cases, with limited resources (Mayosi, et al. 2006; Koech & Ngeno, 2014). In African countries, the direct medical cost of treating one patient with RHD in six years was estimated to be US\$17375 in 1987, increasing to US\$31661 with surgical procedures (Ekra & Bertrand, 1992; Olubodun, 1994). A study that estimated the cost of treating patients with RHD in Nigeria confirmed the equivalence of the burden from treating one patient to the cost of preventing 5.4 cases (Jaiyesimi, 1982). The main burden is the costs of outside referrals that are often required during the course of treatment, adding to the challenges that the health systems of developing countries are confronted with.

As a result, the majority of children and adults in Africa who live with RHD have lost opportunities for prevention because of limited resource allocations towards preventive interventions, such as treatment of sore throat (Cilliers, 2015). This concurs with the findings by Terreri, et al. (2001). The consequence of this limited resources or misallocation to patients and health systems is the high cost of irreversible heart valve damage that can only be alleviated by surgery, if it is available at all (Gunter, Asmera & Parry, 2006; Watkins, et al. 2016).

Another factor impacting the cost estimation of ARF/RHD and causing variation in costs reported across studies was differences in methodology utilised. The absence of standard reporting across all the studies, through mainly a lack of clear descriptions of the cost ingredients, was a notable failure. Studies lack clear and common categories for input or motion cost categories while disaggregating costs, as shown in *table 4*. Furthermore, it was also unclear how the costs were disaggregated when motions comprised personnel in the costs estimation. For instance, several studies provided cost estimation of echocardiographic screening, dispensing penicillin and diagnostic activities including surgery but the personnel costs were not stated clearly. Significantly, studies did not describe what resources compared in surgery or surgical procedures, regardless of surgery being a common category of the RHD burden that demands intense resource usage. In general, ARF/RHD studies to date have focused on the clinical portion of the burden but not the cost analysis and the breakdown of the ingredient costs.

3.3 Interpretation and Implications of Reviewed Studies for This Thesis

It is evident from the current literature that a small body of information exists regarding cost analysis of ARF/RHD in general. This is despite the presence of significant evidence from a wide range of studies on economic evaluation in CVDs, while those that particularly address RHD-related diagnosis are rare globally. In the case of South Africa, no study clearly stipulates the cost of ARF/RHD from a health systems perspective. This gap in information needs attention witnessing. It has been noted that in Cuba the role of economics and economic evaluations are vital in ARF/RHD, thus, the country evidenced dramatically reduced morbidity and premature mortality in children and young adults while reduced 90% of the cost (Watkins,

et al., 2015). It is most important for policy decision making to be dependent on such robust evidence.

Having robust evidence regarding RHD care would assist countries such as South Africa where replacing affected heart valves is expensive but literature addressing estimated amount is rare and unclear. In addition to that, individuals who have undergone surgery also face additional challenges that require more heart operations, making them more susceptible to complex, lifelong heart problems and their attendant costs (Marijon, et al. 2012). Such challenges have potentially been forcing the public health facilities to limit the number of valve surgeries that can be performed. As a consequence, many South Africans die while awaiting valve surgery (Zilla, 2014). Cuba is a model country that has increased the coverage of treating sore throat and introduced ARF interventions and thus seeing RHD expenditure on heart surgery falling by about 90% within a decade following a comprehensive RHD prevention program (Watkins, et al. 2015).

Table 4 presents the summarised unit and/or total costs reported of different countries. The currencies of different nations were first converted to the respective country's local currency using the average exchange rate in the year of study if the United States dollar (US\$) or some other currency is used. Costs were then inflated from the year cost/value presented in the articles to the cost/value of using the respective country's average inflation rate (ratio of CPI in 2017 to CPI in base year), and finally converted to 2017 South African Rand (R) to the United States dollar (US\$) using the 2017 exchange rate.

Table 4: Health systems cost data of ARF/RHD care/treatment (US\$ 2017)

Study author and year	Nation	Study population (n) and group (age)	Sub-condition/prevention/care/treatment type	Costing methods used	Costing Unit	Cost in ZAR 2017)
(Watkins, et al. 2015)	Cuba	n=273933 (age 5 to 24)	Cost of severe RHD hospitalisation	Decision tree model	Per episode	US\$6606.86
(Irlam, et al. 2013)	South Africa	n=97 (age 3- 15)	Daily penicillin + 1 set of lab tests/ECG/echo/CXR	Markov model to assess the cost-effectiveness of care	Per patient	US\$3107.12
(Irlam ,et al. (2013)	South Africa	n=97 (age 3-15)	Inpatient treatment of RHD (7 days admissions)	Markov model to assess the cost-effectiveness of care	Per patient	US\$16776.85
(Irlam, et al. 2013)	South Africa	RHD patients	Lowest cost of Penicillin for acute sore throat	Unclear	Per Patient	US\$11.75

(Milne, et al. 2012)	New Zealand	n=7404 (age - 14 and age 45- 79)	Annual admissions cost for diagnosis of ARF or RHD	Ingredients approach	Per year n=7404	US\$13,528,122.37
(Revees, et al. 2010)	Fiji	n=362 (age 5- 15)	Echocardiographic screening for RHD in schools	Unclear	Per-patient detected	US\$42.03
(Soudasanane, et al. 2007)	India	n=178069 (age 5-15)	surgery at average of per procedure	Ingredients approach	Per patient	US\$1003.24
(Jacqueline, 2002)	USA	n=173 (age 5 - 17)	Treating ARF with antibiotic per episode	Unclear	Per patient	US\$54.39
(Terrerri et al. 2001)	Brazil	n=100 (age less than 18)	Direct cost to public health care provider per episode	Ingredients approach	Per patient	US\$483.88
(Michaud et al. 1999)	USA	n=2000 (3 months to 20 years)	Cost of ARF admission and subsequent care per episode	Unclear	Per-patient per year	US\$14722.75

Most of the studies on the cost of RHD were conducted in middle income and high income countries, with alarming absence of investigative research in highly affected low income countries. Yet, the available evidence indicates that RHD management is expensive, being both a health factor as well as a long term economic burden. In Table 4, the cost components of different RHD related care shows variation in cost depending on the region and country. The USA seems to have the highest cost of ARF admission and subsequent care per episode (US\$14722.75) compared to the US\$6606.86 cost per episode for severe RHD conditions in South Africa. The drivers of cost of RHD care costs in all countries regardless of the unit cost of the care are hospitalisation and surgery in severe cases, while follow up outpatient costs are driven by a cost of RHD medications.

Therefore, it is shocking to witness the absence of economic evaluations (cost analysis) of the disease in lower economic regions to guide governments and policy makers to overcome prevalent barriers to ARF/RHD and its care. Some of the barriers are related to community awareness and the primary healthcare level treatment options that are available, affordable and acceptable (Zuhlke, et al, 2015; Moloi, et al. 2016). Given these barriers and budgetary constraints, it is crucial for public health systems to address these constraints in a contextualised and economically efficient manner (Longenecker, et al. 2014)

4. Conclusion

This literature review stressed about partial economic evaluation studies called cost analysis in ARF/RHD care and studies that reviewed the cost of illness. Evidence shows that ARF/RHD treatment/care and control/prevention costs in LMICs are highly inadequate, mainly in low-income countries. The research shows that global attention regarding the costs of this neglected disease alongside the efforts to scale up treatment and preventions in these settings is limited. Firstly, global attention should be focused on using standard methods of care (i.e. clinical protocol) to create cost information of ARF/RHD treatment and prevention especially to estimate key cost drivers across settings. Secondly, there is a major need to estimate actual resource use and costs in the provision of care, as such information can be used to improve efficiency and budgeting over time, particularly in high ARF/RHD prevalent countries (i.e. low-income). In addition, disease-specific research, such as ARF/RHD cost

estimation, lacks cost input disaggregation mainly the long-term burdens given most individuals practice disease sequelae over time, even after surgery (Marion, et al. 2012).

The African continent where 10% of the world's population resides hosts 50% of the RHD victims who lack an understanding of the needed resources to tackle the ARF/RHD endemic (Ntusi & Mayosi, 2009; Koech & Ngeno, 2014). The literature indicates that to date there has been no full cost analysis (from outpatient to surgery) performed in depth to evaluate the cost of RHD care in South Africa. To this researcher's knowledge, there is no comparative study of cost and cost-effectiveness of different types of RHD preventions (feasibility of primary prevention vis-à-vis secondary and tertiary preventions) for the management of the disease in South Africa. This study has revealed the existence of only two studies that assessed the cost of penicillin and inpatient days cost in the South African context, yet none in the context of other nations. While the gap is substantial and will continue to increase in the absence of concentrated prevention efforts, which could contain costs by reducing future spending on ARF/RHD. The need exists for future cross-country studies on countries such as Ethiopia, Mozambique and Uganda. Ongoing efforts to comprehend the cost of providing ARF/RHD care in these countries will be critical towards attaining universal health coverage (UHC) and improving the overall population health on the continent.

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PART C: JOURNAL MANUSCRIPT

Proposed Journal: BMC public health⁴

⁴ In order to improve readability figures, graphs and tables have been embedded in the text. Yet, some details are added to the appendix section.

The Health System Cost of Rheumatic Heart Disease in the Western Cape Province of South Africa.

Abstract

Background

Rheumatic Heart Disease (RHD) is a disease of poverty that is neglected in developing countries, including South Africa. Lack of adequate evidence regarding the cost of RHD has hindered national and international actions to prevent RHD related deaths. The objective of this study was to estimate the cost of RHD-related health services in a tertiary hospital in the Western Cape, South Africa.

Methods

A mixture of ingredients and step-down costing approaches were used to estimate the cost of RHD care from health system perspective. Health system perspective costing is often used by researchers when there is interest on finding the costs borne by the healthcare provider only (17). All costs were estimated in 2017 (base year) South African Rand (ZAR) and 3% discount

rate in order to allow depreciation and opportunity cost of purchased capital items (13). Data on service utilization rates were collected using a randomly selected sample of 100 patient medical records from the Global Rheumatic Heart Disease Registry (REMEDY) study, a registry of individuals living with RHD. Patient-level clinical data, including, prices and quantities of medications and laboratory tests consumed, were collected from Groote Schuur Hospital (GSH), the main site of cardiac care for these individuals. Step-down costing was used to estimate provider time costs and all other facility costs such as overheads. REMEDY and GSH data were aggregated to estimate the total annual costs of RHD care at GSH and the average annual per-patient cost among REMEDY participants. One-way univariate sensitivity analysis was conducted to deal with uncertainty.

Results

The total cost of RHD care at GSH was estimated at \$2, 238, 294 (ZAR27 million) in 2017, with surgery costs accounting for 65% of total costs. Per-patient average annual costs, which included outpatient care, cardiac medical and intensive care unit (ICU) care, cardiac catheterisation

laboratory (Cath lab) procedures, and heart valve surgery, was estimated at \$4,311 (ZAR52,000) per-patient annually. The cost of medications in outpatient unit care, and consumables related to cardiac catheterisation and heart valve surgery were the main cost drivers.

Conclusion

RHD care consumes a significant level of tertiary hospital resources in South Africa, with annual per-patient costs much higher than many other non-communicable and infectious diseases. This analysis supports the scaling up of primary and secondary prevention programmes at primary health centres in order to reduce the future burden on tertiary services. The study may also inform resource allocation efforts related to RHD at tertiary centres and provide cost estimates for future studies of intervention cost-effectiveness.

Keywords

Unit cost, cost analysis, health systems, provider cost, rheumatic fever, rheumatic heart disease, surgery, tertiary care, cardiology

1. Background

Rheumatic heart disease (RHD) is the most common acquired cardiovascular disease among children and adolescents in developing countries. (1, 3). RHD is a chronic inflammatory disease of the heart valves that result from recurrent episodes of acute rheumatic fever (ARF). Heart valve disease often leads to heart failure, stroke, and premature death including among children and young adults (23). Recent studies have estimated about 33 million prevalent cases and 320,000 deaths from RHD globally in the year 2015 (3, 10). African countries have some of the highest rates of RHD in the world (23). Previous studies in higher-income areas of the world have documented that the cost of RHD is high because most affected individuals experience a lifetime of repeat hospital admissions and expensive surgical care; the physical and psychological impact on patients and households is also significant (2). The condition results in high levels of resource use in ill-equipped and under-financed public health facilities in poor countries (3, 4). Even though surgery can save or prolong life, access remains low in many countries due to lack of early diagnosis and prompt referral – as well as

shortages in surgical services themselves (37).

Lack of information on the cost of RHD is a barrier to equitable allocation of resources to prevent and treat the condition and assess new RHD technologies and interventions through comparative cost-effectiveness analyses (15, 16). A recent review found very few studies on the economics of RHD, and no studies of the cost of care in the African context (38). The objective of the present study is to estimate cost of care for RHD from the public health system (provider) perspective at a tertiary hospital in urban South Africa. This study looks at outpatient costs and inpatient costs at three different levels of care. The study focusses on two topics: (a) estimating the total costs incurred at Groote Schuur Hospital (GSH) in 2017 because of RHD, (b) estimating the per-patient annual cost of care among a representative sample of individuals requiring tertiary care.

2. Materials and Methods

2.1 Ethics Approval

Ethical approval was obtained from the University of the Cape of Human Research Ethics Committee (UCT_HREC Ref:

436/2017) as well as the Western Cape Department of Health (WCDoH) prior to commencement of the study. During the medical records review, privacy of patients was maintained, and no identifying information such as patient participants' names and identity numbers were collected.

2.2 Study Setting and Population

This cross-sectional cost analysis study was carried out in 2017 at GSH, which is a public tertiary level healthcare facility that serves patients of the Western Cape Province and beyond. A devoted cardiac clinic within GSH provides care for cardiac patients (including RHD, ischemic heart disease, heart failure, endocarditis, and more) on average for about 7400 patients annually. Inpatient wards also provide acute care services in a cardiac intensive care unit (ICU), cardiac catheterisation laboratory, and cardiac surgical theatre. In this study, cost data from GSH were complemented with more detailed data on patient utilisation of health services that were obtained from 100 participants in the REMEDY study, an international registry of RHD that includes several hundred cases at GSH (14).

2.3 RHD Pathway of Care

The cardiac clinic (E17) in GSH is the oldest devoted outpatient clinical cardiology service in sub-Saharan Africa. Patients who get diagnosed with RHD in E17 come through different referral pathways such as emergency departments, primary care clinics, and other referral clinics within or outside GSH. Care in E17 is provided by senior registrars, consultants, and registered nurses, among others. RHD patients are identified through detailed investigation of blood, electrocardiogram and echocardiography tests. Stable individuals with RHD are seen on one of three weekdays during which dedicated clinic sessions are held.

Patients with appointments for normal RHD follow-up care first collect their medical record folder from the receptionist then are seen by a nurse who performs routine screening activities and reviews the medical record. Depending on the appointment category (as indicated in the medical record evaluation) and the results from clinical measurements, patients are attended by a registered nurse, registrar, or consultant, or if there are severe or acute issues are referred to the emergency unit or admitted as

inpatients at GSH. Patients with RHD visit GSH as infrequently as twice yearly if they are clinically stable. Routine appointments are given with a one month supply of medications and instructions to return in about 6-12 months unless complications arise. Follow-up appointments are planned to evaluate progression of disease and assess adherence to treatment. Annually, about 100 new patients are enrolled in the RHD clinics at GSH. During the REMEDY study (which recruited 448 participants from 2012 to 2014), staff members reviewed and selected new patient folders for further follow up for research purposes and separately documented usual standard of care (i.e., medications, appointments, contact details) in order to investigate the clinical epidemiology of the disease. The observational REMEDY study did not provide any care to RHD patients; however, they captured major adverse events and instances of defaulting on medications or other aspects of care. Notably, pharmacy (refill) visits are few and are much less resource-demanding compared to clinical follow-ups; often patients collect pre-packed and dispensed medications from a third-party provider. Hence this study did not estimate pharmacy visit costs outside GSH.

2.4 Approach

2.4.1 Overall Approach

A health systems (provider) perspective was adopted. Retrospective costing for patients with diagnosis of RHD was conducted using mix of the ingredients approach and step-down approach by aggregating costs at different levels of care (e.g., outpatient and various inpatient wards). The ingredients approach was generally used to estimate direct costs such as medications, while the latter was generally used to estimate indirect costs. All data were collected from January 2017 to December 2017. Costs were calculated in South African Rand (ZAR) using 2017 as the base year. A standardised set of four data collection instruments was used: one for each of the major clinical units where RHD care is delivered at GSH. These clinical units are: outpatient clinic (E17), medical and ICU ward, cardiac catheterisation laboratory (C25), and surgical theatre (D21).

2.4.1.1 Ingredients Costing

This approach primarily used detailed medical records and observations to measure specific resources required for delivering RHD care. Utilisation patterns of

resources such as, medications, laboratory tests, and diagnostics and consumables related to RHD care were collected. For example, the cost of medications were estimated according to the number of medications recorded as dispensed for each of the 100 REMEDY participants then multiplied by the cost per dosage/injection. Other approaches for determining ingredients used included semi-structured interviews of providers to establish resource use. REMEDY and other hospital medical records were reviewed to establish utilisation rates for specific services, and semi-formal interviews with clinical experts in RHD care were also conducted. The cost share of cardiac medical and ICU care on RHD was calculated using the number of inpatient bed-days at GSH; i.e. by multiplying the number of admissions with the average length of stay. The average length of stay of individuals with RHD in the cardiac wards was 4.73 days per admission according to the most recent annual report.

Price lists were obtained from the Western Cape Department of Health (WCDoH). As per treatment guidelines and the data obtained from medical records, direct medical costs were calculated using the

accounting identity; i.e., costs incurred are the product of prices and quantities of goods and services consumed.

2.4.1.2 Step-down Costing

Step-down costing approach is commonly used to estimate costs that are long-term but not directly related to the patient utilisation, including costs borne by support departments in health facilities (17). Capital costs (e.g., medical building, equipment and furniture) and recurrent indirect costs (e.g., overhead costs incurred by GSH, electricity, water, cleaning, security) of providing RHD care were costed using the step-down approach.

Capital costs and their respective expected life years were obtained from the hospital procurement department. Original costs obtained were also inflated to ZAR 2017 costs using the consumer price index. Specifically, equipment and furniture item costs were apportioned to RHD care according to the share of RHD patients using the items. Building costs were estimated using square meter of space used in RHD care. Costs were calculated by multiplying by the building replacement value per square meter \$3, 206 (ZAR 38,670), which was obtained from the

building and engineering company-approved tender estimate for GSH (22). Recurrent cost data were obtained from the finance department of GSH for the 2016/2017 financial year. As recommended by the World Health Organization (WHO), capital items were discounted and annualized using a discount factor of 3%, reflecting the opportunity cost of purchasing the capital items (13). An estimated lifetime of 30 years for buildings and 10 years for equipment and furniture were used (13, 17). Sensitivity analyses were conducted using 0%, 5% and 10% discount rates with the upper range (10%) corresponding to the maximum discount rate used in cost-effectiveness studies for South Africa to verify the robustness of the results (12, 13, 20, 42).

Costs were categorized into overheads and final service centres (17). The overhead costs include resources that cannot be directly associated to care, while the final service centres include resources used in care (13, 18). Overhead costs comprise cost of general support services departments that are important for the facility to operate (13, 17). These include utilities (i.e. electricity, water), non-clinical personnel (i.e. cleaning, security) as well as

stores that provide non-patient specific services (36). Overhead costs were estimated by assessing the overhead expenditures assuming that all patients utilise equal amount of overhead costs when they visit the healthcare facility during a given period of time (36). The calculation for overhead costs per visit was the annual overhead expenditure divided by annual number of patient visits. This approach was used for both outpatient and inpatient departments of GSH because a cost centre accounting system does not exist in the hospital. Overhead expenditures were allocated directly to outpatients and inpatients departments using an allocation factor based on the patient day equivalent (PDE) concept (17, 36). PDE is estimated as:

$$PDE_{\text{outpatients}} = (\text{annual inpatient days}) \times \frac{1}{\text{weighting factor}} + (\text{annual outpatient visits})$$

$$PDE_{\text{inpatients}} = (\text{annual inpatient days}) + (\text{annual outpatient visits} \times \text{weighting factor})$$

is the local practice at the University of Cape Town is to employ the (empirically-based) rule of thumb that an outpatient visits costs one-third (1/3) of an inpatient

day, and this is used as a weighing factor (36).

Overhead costs per outpatient visit and inpatient day at GSH are thus expressed as:

$$\text{Overhead cost per outpatient visit} = \frac{\text{annual overhead expenditure}}{PDE_{\text{outpatients}}}$$

$$\text{Overhead cost per inpatient day} = \frac{\text{annual overhead expenditure}}{PDE_{\text{inpatients}}}$$

Costs of different centres within GSH that render services to the entire hospital (i.e., intermediate costs) were incorporated in overhead costing; these included the pharmacy and laboratory departments (18). These intermediate and overhead costs were later added to final cost department in gradual manner. Recurrent and capital costs were also allocated to the four clinical units (outpatient, medical and ICU ward, cardiac catheterisation lab, and surgical theatre) directly according to their actual resource utilization. For instance, estimates of square meters of space used directly for care were used to distribute the building costs to the four units. Incurred recurrent and capital costs were distributed according to clinical unit using allocation bases and resource usage. For instance, the number of individuals with RHD as a percentage of total number of

patients served in each clinical unit were used to calculate utilization factor, hence the share of costs allocated to RHD.

There was no cost incurred by GSH for training nurses or other staff personnel specific to RHD, however, lectures were given by senior registrars to nursing staff every Tuesday; nurses also had an opportunity to participate in catheterisation procedures to teach them about post-procedure care.

Finally, step-down cost estimates were added to the ingredients cost estimates to arrive at total costs. The total cost per admission was estimated by multiplying the average cost per inpatient day by the average length of stay. The annual cost of care per-patient at each of the four clinical units was calculated as the product of the unit cost (per encounter) times the annual utilisation rate. The overall annual cost of care per-patient was calculated as the sum of annual costs at each of the four clinical units. For comparison, the total cost of providing RHD care at GSH in 2017 was extracted from the spreadsheets as the aggregate costs at each of the four clinical units (i.e., the costs required to deliver care for all individuals with RHD, including but not limited to the 100 REMEDY participants).

2.4.1.3 Personnel Costing

Statistics regarding time allocation, and time spent by different personnel providing care or consulting patients were not available at GSH. Particularly how long a service takes to deliver, hence the proportion of each staff member's salary allocated to RHD care. Additional information was obtained from key clinical/hospital experts and ward operational managers through non-formal interview and review of their weekly duty excel spreadsheets. Eight non-participatory observations were conducted to understand patient management and staff time allocation and to identify and examine the costs involved. The limitation of this strategy is that responses could not be authenticated through time-motion studies hence it might over or underestimate the share of time spent on providing RHD related care.

2.5 Data Analysis

Study data was entered into Microsoft Excel for quality evaluation then later imported into STATA 14 (Statacorp, 2015). Descriptive statistics (means, proportions, etc.) were used to assess participants' demographic characteristics.

2.5.1 Sensitivity Analysis

In order to assess the impact that changes in assumptions or parameters would have on final cost estimates, one-way deterministic sensitivity analysis was performed. The following cost model inputs were varied: (a) discount rate of 0%, 5% and 10% on capital costs (19, 20); and (b) utilisation rates of the four clinical units were varied from base values to lower and upper 95% confidence interval estimates (per the REMEDY database) to examine their effect on average annual per-patient costs (21).

3. Results

3.1 Baseline characteristics of the study sample costs

The demographic characteristics of the study participants are provided in *table 5*. A majority of the participants were female (67%); with current age of the patients varying from to 24 to 81 years old. Participants were predominately from low-income backgrounds, and most were unemployed. Forty-eight percent had valve surgery at some point in their lifetime, ranging 1980 to 2016. In 2016 the cardiac surgery theatre at GSH performed 322 valve replacements, 56 of which were RHD related. The most common valve

replacement types were aortic (46%), mitral (41%), and mixed aortic and mitral (13%).

Table 5: Demographic characteristics of 100 individuals with RHD participating in the REMEDY study

Population description	Study population outcome
Mean age	47.5 years
Gender	67 % Female 33 % Male
Marital status	52% Married 40% Never married 7% Widowed 1% Divorced
Employment history	17% Employed 1% Self-employed 83% Unemployed
Educational background	2% No formal education 3% Primary level 81% Secondary level 4% Tertiary level

3.2 Costs of RHD Management from Provider Perspective

3.2.1 Annual Per-Patient Cost of RHD Care

The REMEDY database provided the number of visits and admissions for the 100 patients that attended cardiac care at GSH. Utilisation data were collected over two consecutive years to capture longer-term rates in clinically stable patients who only attend outpatient clinics (i.e., less frequently) (*table 6*).

Table 6: Average annual utilisation rates for RHD care at four clinical units at GSH

Clinical unit	Outpatient clinic	Medical and ICU	Cath lab	Surgery/theatre
Per-patient utilisation rate per year	2.9	0.31	0.19	0.22
95% confidence interval	(2.0 - 3.9)	(0.11 - 0.50)	(0.068 - 0.31)	(0.043 - 0.39)

Summaries of average annual per-patient costs for the four different clinical units (outpatient, ICU, cardiac cath lab, and surgical theatre) are provided in tables 7, 8, 9 and 10, respectively. The cardiac medical and ICU care average unit outpatient accounted smallest portion of the average annual total costs for RHD care. Medications and staff costs were the driver of total costs of outpatient visits

while blood transfusions and staff costs in inpatient medical and ICU care were the highest. Consumables costs were the drivers in the cardiac catheterisation laboratory and surgical theatre.

The cost of routine medications was the major cost driver in outpatient clinic care (67%) followed by staff time (16% of cost). In the cath lab and surgical theater, consumables (such as prosthetic valves and specialised catheters) were the major driver (51% and 44%) respectively. Table 7-10 show detailed annual per-patient costs that comprise the weighted average cost.

As seen in *table 11*, RHD care costed GSH an estimated \$2, 238, 294 (ZAR27 million) in 2017. The average cost per patient-year, based on utilisation data from the REMEDY study, was an estimated \$4, 311 (ZAR52 000).

Table 7: Outpatient total and unit costs

Cost component	Annual total cost to GSH in 2017 (ZAR)	Unit cost per encounter in 2017 (ZAR)
Step-down costing		
Personnel	R 2 300 000	R 670
Overheads	R 250 000	R 72
Maintenance	R 30 000	R 10
Consumables	R 105 000	R 31
Building	R 300 000	R 90
Equipment & furniture	R 140 000	R 40

Sub-total	R 3 200 000	R 920
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Ingredients costing		
Medications	R 1 950 000	R 2900
Laboratory tests	R 320 000	R 470
Sub-total	R 2 300 000	R 3 400
Total cost	R 5 500 000	R 4 300

Table 8: Cost of medical and ICU care

Cost component	Annual RHD care total cost to GSH in 2017 (ZAR)	Unit cost per encounter in 2017 (ZAR)
Step-down costing		
Personnel	R 1 100 000	R 590
Overheads	R 422 000	R 230
Maintenance	R 50 000	R 26
Consumables	R 320 000	R 170
Building	R 490 000	R 260
Equipment & furniture	R 40 000	R 85
Sub-total	R 2 500 000	R 1 360
Ingredients category		
Medications	R 130 000	R 430
Blood transfusions	R 185 000	R 600
Sub-total	R 350 000	R 1050
Total cost	R 3 000 000	R 2 400

Table 9: Cost of catheterization laboratory care

Cost component	Annual RHD care total cost to GSH in 2017 (ZAR)	Unit cost per encounter in 2017 (ZAR)
Step-down costing		
Personnel	R 1 200 000	R 3 800

Maintenance	R 41 000	R 130
Consumables	R 4 100 000	R 13 000
Building	R 407 000	R 1 300
Equipment & furniture	R 295 000	R 5 540
Sub-Total	R 6 100 000	R 24 000
Ingredients category		
Medications	R 520 000	R 1 700
Total cost	R 6 200 000	R 25 500

Table 10: Surgery total and unit costs

Cost component	Annual RHD care total cost to GSH in 2017 (ZAR)	Unit cost per encounter in 2017 (ZAR)
Step-down costing		
Personnel	R 2 800 000	R 31 000
Maintenance	R 61 000	R 670
General consumables	R 850 000	R 9 100
Perfusion consumables	R 3 400 000	R 37 000
Anaesthesia Consumables	R 240 000	R 2 700
Prosthetic heart valves	R 1 200 000	R 13 000
Building	R 610 000	R 6 700
Equipment & furniture	R 1 100 000	R 41 000
Sub-total	R 11 000 000	R 142 000
Ingredients category		
Theatre medications	R 600 000	R 11 000
Average annual per-patient theatre cost	R 12 000 000	R 153 000

Table 7: Summary costs: Aggregate costs to GSH in 2017 and estimated annual costs per-patient

Clinical unit	Aggregate cost to GSH in 2017 (ZAR)	% share of aggregate total cost	Estimated per-patient annual cost (ZAR)	% share of per-patient annual cost
Outpatient clinic	R 5 500 000	21%	R 12 500	24%

Cardiac medical ICU and ward	R 3 000 000	11%	R 800	2%
Cardiac catheterisation lab	R 6 600 000	23%	R 4 900	9%
Surgical theatre	R 12 000 000	45%	R 34 000	65%
Total	R 27 000 000		R 52 000	

3.3 Sensitivity Analysis

3.3.1 One-Way Univariate Sensitivity Analysis

Figure 3 demonstrates the effects that varying utilisation rates at each of the four clinical units had on overall annual average per-patient costs. The costs were relatively

less sensitive to variations in the discount rate (figure 4). In both sets of analyses, the influence of the parameters was largest on surgical theatre costs, since this was the most expensive clinical unit.

Figure 3: Sensitivity analysis: variation in utilisation rates and their effect in annual cost of RHD per-patient

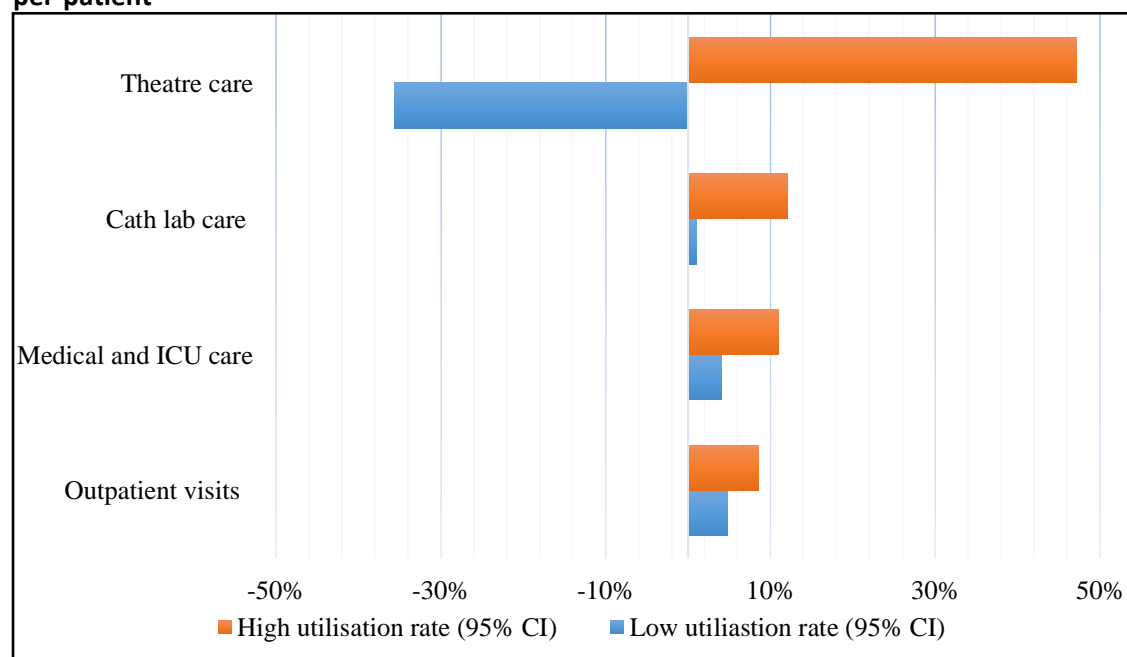
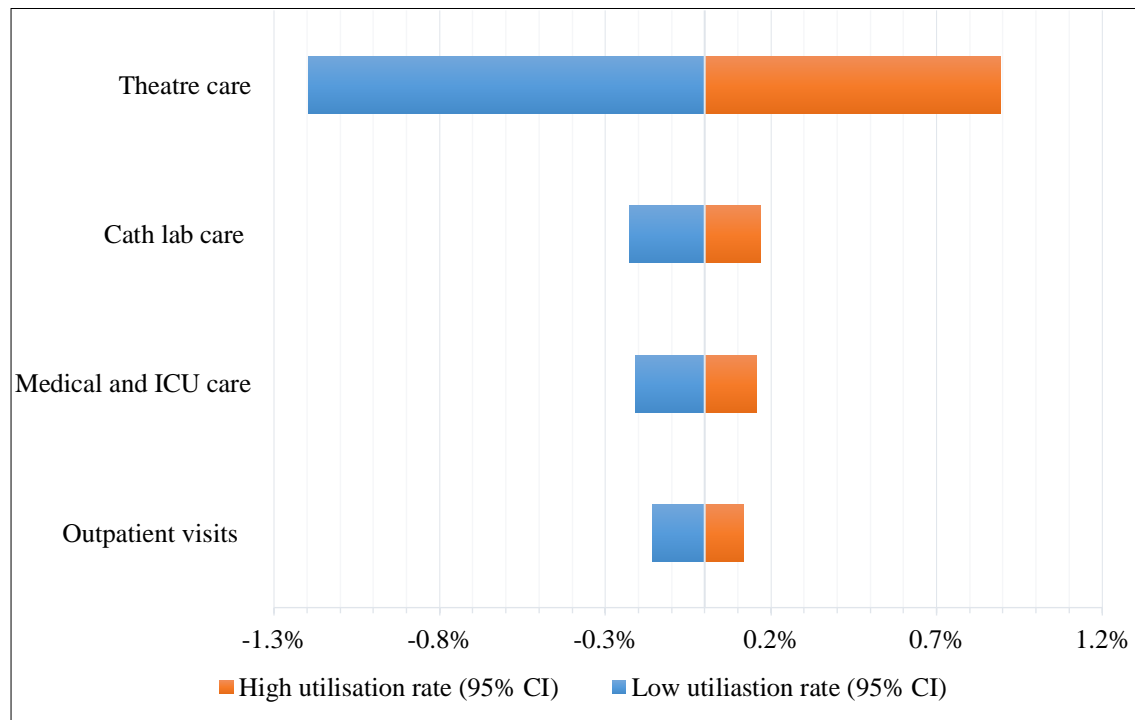


Figure 4: Sensitivity analysis: variations in discount rates and their effect on annual cost of RHD per patient



4. Discussion

This cost analysis sought to estimate, from the provider perspective, the annual cost of RHD care in a tertiary centre in the Western Cape Province of South Africa. RHD was estimated to cost GSH about \$2, 238, 294 (ZAR34 million) in the year 2017. Triangulating these estimates with data from the REMEDY registry, RHD was estimated to cost \$4, 311 (ZAR52,000) per-patient per year in total, with most of the total cost being driven by surgical theatre and cardiac catheterisation laboratory costs. This tertiary hospital based study indicates that average per-patient cost of RHD ZAR52, 000 (\$4, 311) was much higher

than the average annual per capita income of ZAR12, 860 (\$1, 064) of a South African individual (44). On the other hand, RHD cost was also much higher than the cost of the facility-level care delivery of HIV/AIDS, drug sensitive tuberculosis, and hypertension, which have been estimated at 2016 \$663 (ZAR8000) (41), 2015 \$249 (ZAR3000) (42) and 2016 \$249 (ZAR3100) (43) per year, respectively. Although managing RHD costs more on a per-patient basis than all three of these conditions, it has been the most neglected (9).

This study is the first of its kind in the African context. As summarised in a recent review, there have to date been no costing studies on RHD in Africa, and in fact, only

one prior costing study has been conducted in a developing country setting. Terreri et al., looking at RHD in Brazil, quantified per-patient direct costs of RHD and rheumatic fever from the provider perspective using the ingredients approach (1). Even after adjusting to a common currency and year, the cost estimates in this study are higher than in the Brazilian study, probably due to advances in care (i.e. new technologies) and to the fact that health sector prices tend to rise faster than inflation. In addition, the present study took a more detailed look at surgical care, the most expensive aspect of RHD care.

This study assessed the cost of RHD to the public sector. It did not include ambulatory costs or admission costs from the private sector. It also did not look at patient costs, including so-called “direct non-medical costs” like transport and food, which – from a societal perspective – are a significant share of healthcare costs in South Africa (36, 40). However, the direct medical costs were still substantial, and from a societal perspective, the cost of surgical care from the provider perspective is probably the largest single driver of costs.

It should be noted that the main cost contributors to outpatient RHD care were monthly medications cost followed by personnel cost. While major drivers for personnel costs were the major cost driver for inpatient medical and ICU ward care. These findings are similar to a study from Australia in which two-thirds of the cost of ICU care in tertiary hospitals was related to personnel (27). Rechner and Lipman (2005) predicted that consumables expenditure (in general) is likely to increase in the future in light of new innovations and therapies. Along these lines, the cardiac catheterisation laboratory and surgical theatre consumables were found to be major drivers of cost in this study. One implication of this study is that research on developing cheaper, locally made prosthetic valves and catheters should be supported, and measures should be taken to support the production and export of such products to other African countries (39).

This study can also be viewed as an analysis of the economic consequences of inadequate prevention of rheumatic fever and RHD. RHD can be completely prevented by addressing bacterial sore throat in children using primary health centre-based approaches. When this

prevention window is missed, RHD develops and inevitably leads to heart valve damage, requiring one or more surgeries over the lifetime of most individuals. Several programmes in the Latin America region demonstrated reductions in healthcare costs from RHD of over 90% when comprehensive prevention efforts were undertaken (11). However, barriers such as shortage of skilled staff, poor public awareness about diagnosis and treatment of sore throat and poor access to primary care hindered wide adoption of primary prevention of the disease in South Africa (29) regardless of a plan to roll out comprehensive ASAP programme. This calls for policy implications for priority settings (such as Soweto) to improve community awareness and capture contemporary data on clinical course, complications and treatment practices between patients (14). One crucial aspect of ASAP is advocacy where disease notification is compulsory, yet the legal requirement to notify is neither been stressed nor implemented correctly resulting in poor capture of the disease burden (31). It is recommended for the department of health to establish a pilot web-based notification method in order to explore online notification submissions.

Given the barriers, the present study cost estimates suggest that high cost burden of RHD will be reduced by reducing risk factors of AFR and increasing funds for ARF/RHD control measures. Mainly, the Western Cape Department of Health, and the NDoH to scale up RHD prevention efforts established on the best evidence-based interventions in South Africa.

5. Limitations

This study was a hospital-based cost analysis study with the usual limitations of such a study design. One hundred patient records were reviewed; however, some details were missing, while those with severe disease were often presented with little detail. Nevertheless, considerable effort was taken to produce accurate and relevant estimates. There were a few other limitations to collecting information. First, the medication records did not disaggregate drugs related to RHD from drugs with other indications. Second, out of the 100-participant sample, only 88 individuals were consistently engaged in RHD care in GSH. This finding raises the question of whether they were receiving care elsewhere and thus our costs were underestimates. Third, the step-down approach is not ideal for estimating some

costs such as diagnostics (echocardiography, etc) and pharmacy costs; better data would allow for more precise estimates of these costs using an ingredients approach. In addition, the cost of pharmacy services is likely to be higher at GSH than at health facilities in the community where most individuals with RHD receive the majority of their monthly prescriptions. Overall average annual per-patient care costs are probably inflated compared to what they would be if referring hospitals and clinics had been sampled.

6. Conclusion

Despite its limitations, this study provides crucial contributions to the modest literature on the economics of RHD. It can serve as an input to future economic evaluations focused on RHD programmes and interventions in South Africa. It has also developed a costing framework and data collection tools that can be expanded to other aspects of RHD prevention and care as well as replicated in other African settings. The systematic and widespread collection of data on the cost of RHD will be a key component of raising awareness on the importance of the condition in

Africa and of making the case for investing in RHD prevention.

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Part D- POLICY BRIEF



Rheumatic heart disease (RHD) management and cost of tertiary level care in South Africa

How much does it cost the Western Cape government to provide RHD care at a tertiary hospital?

What is the economic burden of RHD on the public health system of South Africa?

(By Assegid Hellebo)

Key points

- ✓ RHD is preventable, yet it continues to impose high financial and economic burden on the health systems of developing countries, and it is associated to more costly conditions (i.e. cardiac heart failure, stroke and premature death).
- ✓ The estimated expenditure on RHD care at Groote Schuur Hospital in 2017 was \$2, 238, 294 (ZAR27 million).
- ✓ It costs about \$4, 311 (ZAR52, 000) on average per-patient annually to deliver tertiary-level services to individuals with RHD.
- ✓ Medication and consumable costs are the major drivers of outpatient and inpatient RHD care respectively.
- ✓ Primary and secondary RHD prevention measures have not been fully implemented in South Africa. Closing these prevention gaps is an urgent priority if the high costs of tertiary level care are to be reduced.

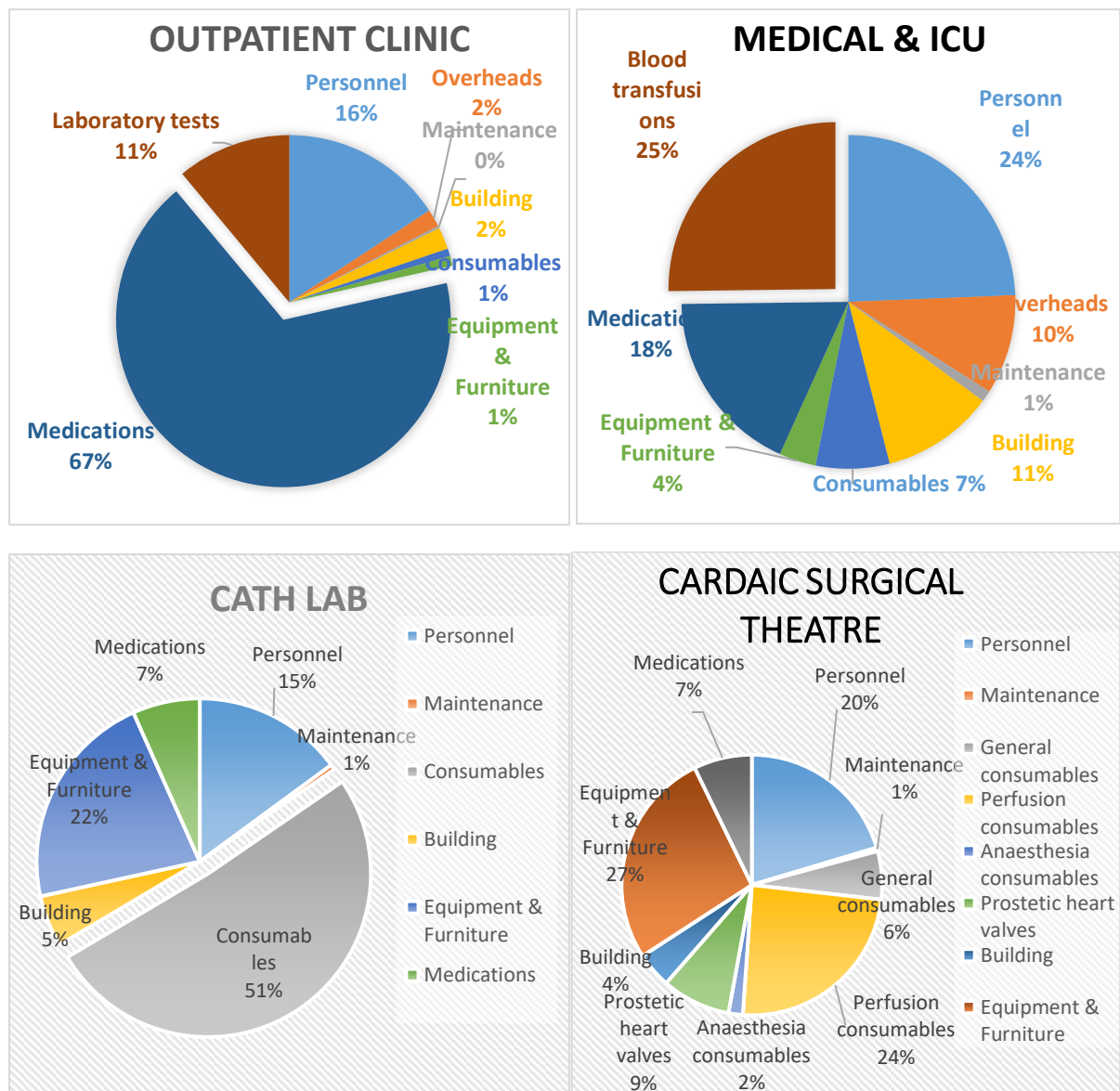
1. RHD and the Health System in South Africa

The legacy of Apartheid has left South Africa with a health system that is inequitable, with the minority having disproportionate access to health services, leading to a situation where preventable diseases of poverty persist in low-income communities (Coovadia et al., 2009). Rheumatic heart disease (RHD) is a classic disease of poverty that is preventable by prompt delivery of preventive measures (sore throat treatment) in primary health centres. According to Drakensberg declaration of 2005, RHD is an important but neglected cause of cardiovascular disease in South Africa, especially among women and children (Mayosi et al., 2006). Globally, RHD accounts for 320,000 deaths annually (Naghavi et al., 2015). Recent evidence suggests a decline of RHD mortality in South Africa, though its incidence and prevalence have remained stable, placing a higher burden on the health system to provide chronic care (Zühlke et al., 2015; Mayosi, 2016). However, little is known about the cost of RHD care from the perspective of the South African government, which limits the public sector's ability to allocate resources and assess new RHD technologies and interventions through comparative cost-effectiveness analyses (Irlam et al., 2015). This policy brief summarises a cost analysis study that was conducted at Groote Schuur Hospital (GSH) in Cape Town

2. Study Methods and Findings

This was a cost analysis from the provider perspective. Patterns of RHD care at GSH were assessed for 100 patients participating in an RHD registry. A combination of step-down and ingredients costing approaches was used. The total cost of providing RHD care at GSH in 2017 was about \$2, 238, 294 (ZAR27 million). The cost of surgery accounted for 65% of total costs, and consumables such as cardiac catheters and prosthetic valves were the major drivers of cost. The breakdown of cost components is shown in *figure 5*. The estimated cost per-patient per year was \$4, 311 (ZAR52, 000); again, most of this cost was due to surgical and cardiac catheterisation services.

Figure 5: Distribution of cost components of RHD care at four clinical



3. Policy Implications

In order to reduce the cost burden of RHD, the following policy interventions could be considered:

- Comprehensive efforts could be undertaken to raise public and health professional awareness about the causes and consequences of RHD, stressing its preventable nature
- The Department of Health could double down on investments in primary healthcare in order to achieve full population coverage of RHD prevention services. District and provincial level RHD registers could be supported in order to track patients early in the disease process and deliver preventive care that can delay or reduce the need for cardiac surgery.
- Medications and consumables (including prosthetic heart valves) were major drivers of the cost of tertiary RHD care. The Department of Health could provide more support to academic and private sector research and development efforts that could eventually lead to cheaper alternatives.

4. Conclusion

RHD is a preventable cause of heart disease in South Africa that predominately affects children and working-age adults. Providing tertiary care is very expensive, at about \$4, 311 (ZAR52, 000) per-patient per year. Most of the current expenditure on RHD is avoidable, since highly effective preventive interventions exist. Conversely, failure to mitigate the disease in its earlier stages leads to higher costs to government. This study, the first of its kind in South Africa, can inform the allocation of resources for RHD prevention and care.

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PART E: APPENDICES

Appendix A: Data Collection Process Outline

The data collection process will make use of data collection and management tool called Microsoft Excel (Microsoft Corporation, USA) in order to perform an organized gathering of information. Section A, B, C and D illustrates what data will be extracted from REMEDY study folders and/or database as well as the pricing of the quantities utilised by respective patients within the hospital.

Section A: RHD Patient Identification/Information

A1. Selected patient code:

A2. Age: (years)

A3. Gender: Male

Female

Is this participant pregnant? No

Yes

A4. Disease severity Mild Moderate Severe

A5. Surgery performed No

Yes

How many times

Section B: Estimating Qualities of Resources Consumed by RHD Patients

B1. Information on record - hospital visits

B1.1	Patient code	
B1.2	Date of first diagnosis	___/___/___
B1.3	Date of first treatment	___/___/___
B1.4	How was the RHD patient diagnosed?	<p>a) Having symptoms (e.g. dry coughing)</p> <p>b) Routine screening in nearest clinic</p> <p>c) Routine screening in community/school</p> <p>d) Diagnosed for RHD while in clinic/hospital for other symptoms/disease</p>

Note down the existing medication routine of the patient for RHD care

B1.4.1 Patient code	B1.4.2 Medication name	B1.4.3 Dosage/quantity	B1.4.4 Rate/Frequency

a) Quantity estimation for outpatient visits

Unit/section	Estimating quantity of resources/services utilized
Consultation time (CT)	Time motion determined from non-participatory observation. Staff time spent per patient
Admission time (AT)	Time motion determined from non-participatory observation. Staff time per spent patient

Drugs and other medical supplies (consumables)	Total quantity of the drugs, syringes, cotton amount utilized per-patient
Laboratory tests	Total number of laboratory tests acquired per-patient

b) Quantity estimation for inpatient visits

Unit/section	Estimating quantity resources/services utilized
Inpatient visit days (IVDs)	Subtract a day a patient admitted (a) from a day discharged (b). Therefore, IVDs= $\sum(b-a)$
- IVDs hospitalization items	Different indirect costs per inpatient days will be estimated using the actual resource (overheads) usage such as; building space and equipment's. (<i>overheads costing explained in section C below</i>)
Transport	Once we establish that specific patient was transported by ambulance as result of RHD or at least diagnosed for RHD after he/she arrived at the facility, we will obtain data from vehicle logbook. This will provide as the kilometres (KMs) travelled per patient, and we sum then up.
Equipment	We will assume that equipment such as (bed, computers, cleaning machines) are assigned to the unit/section or each ward on the basis of inpatient days. The quantity allocation of resource utilisation will be obtained by dividing the amount of days/hours from inpatient visit to the lifetime of the respective equipment.
Food	We assume that food is provided 3 times a day. However, we will engage with the respective hospital to confirm on the matter. To estimate the quantity of resource usage, we will multiply the number of food provided per day by the inpatient days.

Laundry service	Laundry service utilisation will be apportioned to the unit/section on the basis of occupied bed days the same as the respective cost.
Cleaning service	Will be allocated on the basis proxy quota of floor space and the respective usage.

Section C: Estimating Qualities of Overhead Resources Consumed by RHD Patients

Overheads	Quantity estimation
Buildings	<ul style="list-style-type: none"> ➤ Will be determined by means of annuity costs which refers to the current value of the buildings. ➤ If the current value of the buildings is not on a record, we will estimate the costs based on the yearly building maintenance costs which we expect to acquire from the financial accounts GSH hospital ➤ If the annuity costs for GSH hospital is available, we will utilize sum of annuity costs and yearly maintenance costs of this section of the hospital and divide by the number of RHD consultations per year which will be obtained from patient utilization of REMEDY study database.
Vehicles	<ul style="list-style-type: none"> ➤ Includes the cost of vehicles and cost of operating, maintaining and repairing, estimated through annuity function and yearly maintenance costs divided by amount of KMs driven per year. ➤ Operation costs will be examined using obligation registers, or similar records using

	<p>hospital vehicle logbook, which often details the amount of kilometres travelled and the purpose of each journey</p>
<p>Furniture</p>	<ul style="list-style-type: none"> ➤ Costs per test will be estimated based on replacement value (determined by annuity function) and yearly maintenance costs divided by the number of tests executed per year. ➤ Replacement values can be obtained from hospital accounts, local suppliers, or manufacturers. ➤ Finally we will allocate and estimate cost per activity by dividing the amount of days/hours the equipment lifetime be to the amount of days/hours utilized per patient.
<p>Medical Equipment</p>	<ul style="list-style-type: none"> ➤ This includes use of the laboratory and radiology facility including ultrasonography which will be measured through detailed re-enactment of the patients procedures undergone. ➤ If not available the laboratory overhead costs will be estimated using 5% of all the capital items in the laboratory.

Section D: Cost/Price Estimation Procedures for Direct and Indirect RHD Care

Cost Component	Methodology	Required data	Calculations
Direct cost of RHD - Staff (Admin, consultation, HR) - Drugs and test consumables - Equipment (furniture, medical equipment)	Ingredient approach	Productive working hours and minutes spent by the staff members per RHD patient	Hours or minutes spent per patient with RHD multiplied by the respective price (average salary of the respective staff)
	Ingredient approach	The unit price per drug/consumables per RHD patient	The unit price per drug/consumables multiplied by utilisation per RHD patient
	Ingredient approach	Purchasing value of each equipment, interest rate, life years, maintenance costs, total yearly utilisation of equipment for all RHD patients, utilisation per RHD patient	Payment annuity (PMT ^a) = (equipment prices, life years, interest rates) plus maintenance costs/total yearly equipment utilization = (equipment cost per test) multiplied by utilisation per RHD patient
Indirect cost of RHD - Buildings, cars and overheads	Step-down approach	Total inpatient day/days costs of hospital, total number of inpatient days caused by RHD	Total indirect costs of hospital divided by total number of inpatient days because of RHD

Appendix B: Observation Tool

Section A: Estimating Waiting Times and Consultation Times

Observation date:	____/____/____
Facility:	
Observer's name	

Unit/Section	Time patient arrived to the office/unit/Section of staff or start time of the staff(a)	Time the staff finalized treating/duty per-patient or end time of the staff (b)	Total time spent (length of stay) (b-a)
Admission			
medical officers			
Pharmacy			
Others units/sections			
1.			
2.			

Appendix C: Search Strategy

Section A: Search Report: Studies of Cost of ARF and/or RHD Searches June 2017

Search number	Date searched	Database search	Hits (prior to unrelated and/or duplicate articles removal)	Final hits results (after removing unrelated and/or duplicate articles)
1	30/06/2017	PubMed (NCBI)	388	22
2	30/06/2017	Scopus	64	3

3	04/07/20 17	EBscoHost(CINAHAL)	12	2
4	04/07/20 17	EBscoHost (EconLit)	1	0
5	04/07/20 17	EBscoHost (Africa wide information)	4	1
6	03/07/20 17	Central Cochrane	13	1
			Total search= 481	Total references= 29

PubMed (NCBI)

#43 Search (((((((((((("Rheumatic Heart Disease"[Mesh]) OR "Rheumatic Fever"[Mesh]) OR rheumatic heart disease[Text Word]) OR acute rheumatic fever[Text Word]) OR rhd[Text Word]) OR infective endocarditis[Text Word]) OR bacterial endocarditis[Text Word]) OR neglected heart disease[Text Word]) OR rheumatic fever[Text Word]) OR rheumatic disorder[Text Word]) OR arf[Text Word])) AND (((((((((((("Costs and Cost Analysis"[Mesh])) OR cost[Text Word]) OR "Cost of Illness"[Mesh]) OR costs[Text Word]) OR "Economics"[Mesh]) OR economics[Text Word]) OR economic burden[Text Word]) OR total burden[Text Word]) OR economic evaluation[Text Word]) OR economic analysis[Text Word])) AND (((((((("Delivery of HealthCare"[Mesh]) OR "Health Care Sector"[Mesh]) OR ("Health Care Economics and Organizations"[Mesh])) OR health systems[Text Word]) OR health care system[Text Word]) OR health sector[Text Word]) OR health care provider[Text Word])

#42 Search (((((((((((("Rheumatic Heart Disease"[Mesh]) OR "Rheumatic Fever"[Mesh]) OR rheumatic heart disease[Text Word]) OR acute rheumatic fever[Text Word]) OR rhd[Text Word]) OR infective endocarditis[Text Word]) OR bacterial endocarditis[Text Word]) OR neglected heart disease[Text Word]) OR rheumatic fever[Text Word]) OR rheumatic disorder[Text Word]) OR arf[Text Word])) AND (((((((((((("Costs and Cost Analysis"[Mesh])) OR cost[Text Word]) OR "Cost of Illness"[Mesh]) OR costs[Text Word]) OR "Economics"[Mesh]) OR economics[Text Word]) OR economic burden[Text Word]) OR total burden[Text Word]) OR economic evaluation[Text Word]) OR economic analysis[Text Word])) AND (((((((("Delivery of HealthCare"[Mesh]) OR "Health Care Sector"[Mesh]) OR ("Health Care Economics and

Organizations"[Mesh])) OR health systems[Text Word]) OR health care system[Text Word])
OR health sector[Text Word]) OR health care provider[Text Word]) Sort by: [pubsolr12]

#41 Search (((((((("Delivery of Health Care"[Mesh]) OR "Health Care Sector"[Mesh]) OR ("Health
Care Economics and Organizations"[Mesh])) OR health systems[Text Word]) OR health care
system[Text Word]) OR health sector[Text Word]) OR health care provider[Text Word]

#40 Search (((((((("Costs and Cost Analysis"[Mesh])) OR cost[Text Word]) OR "Cost of
Illness"[Mesh]) OR costs[Text Word]) OR "Economics"[Mesh]) OR economics[Text Word]) OR
economic burden[Text Word]) OR total burden[Text Word]) OR economic evaluation[Text
Word]) OR economic analysis[Text Word]

#39 Search health care provider[Text Word]

#38 Search health sector[Text Word]

#37 Search health care system[Text Word]

#36 Search health systems[Text Word]

#35 Search "Health Care Economics and Organizations"[Mesh] Sort by: [pubsolr12]

#33 Search "Health Care Sector"[Mesh] Sort by: [pubsolr12]

#31 Search "Delivery of Health Care"[Mesh] Sort by: [pubsolr12] #29 Search economic
analysis[Text Word]

#28 Search economic evaluation[Text Word]

#26 Search total burden[Text Word]

#25 Search economic burden[Text Word]

#24 Search economics[Text Word]

#23 Search "Economics"[Mesh] Sort by: [pubsolr12]

#21 Search costs[Text Word]

#20 Search "Cost of Illness"[Mesh] Sort by: [pubsolr12]

#18 Search cost[Text Word]

#17 Search "Costs and Cost Analysis"[Mesh] Sort by: [pubsolr12]

#15 Search (((((((("Rheumatic Heart Disease"[Mesh]) OR "Rheumatic Fever"[Mesh]) OR
rheumatic heart disease[Text Word]) OR acute rheumatic fever[Text Word]) OR rhd[Text
Word]) OR infective endocarditis[Text Word]) OR bacterial endocarditis[Text Word]) OR
neglected heart disease[Text Word]) OR rheumatic fever[Text Word]) OR rheumatic
disorder[Text Word]) OR arf[Text Word]

#14 Search arf[Text Word]

- #13 Search rheumatic disorder[Text Word]
- #12 Search rheumatic fever[Text Word]
- #11 Search neglected heart disease[Text Word]
- #10 Search bacterial endocarditis[Text Word]
- #9 Search infective endocarditis[Text Word]
- #8 Search rhd[Text Word]
- #7 Search acute rheumatic fever[Text Word]
- #5 Search rheumatic heart disease[Text Word]
- #4 Search "Rheumatic Fever"[Mesh] Sort by: [pubsolr12]
- #2 Search "Rheumatic Heart Disease"[Mesh] Sort by: [pubsolr12]

Scopus

((TITLE-ABS-KEY (*"acute rheumatic fever"*) OR TITLE-ABS-KEY (*arf*) OR TITLE-ABS-KEY (*"bacterial endocarditis"*) OR TITLE-ABS-KEY (*"infective endocarditis"*) OR TITLE-ABS-KEY (*"neglected heart disease"*) OR TITLE-ABS-KEY (*"rhd"*) OR TITLE-ABS-KEY (*"rheumatic disorder"*) OR TITLE-ABS-KEY (*"rheumatic fever"*) OR TITLE-ABS-KEY (*"rheumatic heart disease"*)))

AND

((TITLE-ABS-KEY (*"cost analysis"*) OR TITLE-ABS-KEY (*cost**) OR TITLE-ABS-KEY (*"economic analysis"*) OR TITLE-ABS-KEY (*"economic burden"*) OR TITLE-ABS-KEY (*"economic evaluation"*) OR TITLE-ABS-KEY (*economics*) OR TITLE-ABS-KEY (*"total burden"*)))

AND

((TITLE-ABS-KEY (*"delivery of health care"*) OR TITLE-ABS-KEY (*"health care economics"*) OR TITLE-ABS-KEY (*"health care provider"*) OR TITLE-ABS-KEY (*"health care sector"*) OR TITLE-ABS-KEY (*"health care system"*) OR TITLE-ABS-KEY (*"health sector"*) OR TITLE-ABS-KEY (*"health systems"*)))

EBscoHost (Africa Wide Information, CINAHL, EconLit)

- | | |
|-----|--|
| S28 | S12 AND S19 AND S27 |
| S27 | S20 OR S21 OR S22 OR S23 OR S24
OR S25 OR S26 |
| S26 | health systems |

S25	health sector
S24	health care system
S23	Health Care Sector
S22	health care provider
S21	Health Care Economics
S20	Delivery of Health Care
S19	S13 OR S14 OR S15 OR S16 OR S17 OR S18
S18	total burden
S17	Economics
S16	economic evaluation
S15	economic burden
S14	Cost*
S13	Cost Analysis
S12	S1 OR S2 OR S3 OR S4 OR S5 OR S7 OR S8 OR S10 OR S11
S11	Rheumatic Heart Disease
S10	Rheumatic Fever
S9	rheumatic disorder
S8	rheumatic disorder
S7	rhd
S6	neglected heart disease
S5	neglected heart disease
S4	infective endocarditis
S3	bacterial endocarditis

S2

arf

S1

acute rheumatic fever

Central Cochrane:

acute rheumatic fever OR arf OR bacterial endocarditis OR infective endocarditis OR neglected heart disease OR rhd OR rheumatic disorder OR rheumatic fever OR rheumatic heart disease in Title, Abstract, Keywords

and

cost analysis OR cost* OR economic analysis OR economic burden OR economic evaluation OR economics OR total burden in Title, Abstract, Keywords

and

delivery of health care OR health care economics OR health care provider OR health care sector OR health care system OR health sector OR health systems in Title, Abstract, Keywords

(Word variations have been searched)

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Appendix D: UCT Ethics Approval Letter (HREC)



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



Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: sunayah.ariel@uct.ac.za

Website: www.health.uct.ac.za/fhs/research/humanethics/forms

28 July 2017

HREC REF: 436/2017

Dr O Alaba

Division of Health Economic Unit
Public Health & Family Medicine
Falmouth Building

Dear Dr Alaba

PROJECT TITLE: THE ECONOMIC IMPACT OF RHEUMATIC HEART (RHD) ON THE HEALTH SYSTEM OF SOUTH AFRICA (Master's candidate-A Hellebo)

Thank you for your response, addressing the issues raised by the 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 the 30th July 2018.

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)

We acknowledge that the following student: - Assegid Hellebo will also be involved in this study.

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.

Yours sincerely

PP *UBurgess*

PROFESSOR M BLOCKMAN

CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.

Institutional Review Board (IRB) number: IRB00001938

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 Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH

HREC 436/2017

Appendix E: Western Cape Government Approval Letter



GROOTE SCHUUR HOSPITAL

Enquiries: Dr Bernadette Eick
E-mail : Bernadette.Eick@westerncape.gov.za

Dr O. Alaba
Division of Health Economics Unit
Public Health & Family Medicine

E-mail: jesi.zuhike@uct.ac.za / olufunke.alaba@uct.ac.za / HLLASS001@myuct.ac.za

Dear Dr Alaba

RESEARCH PROJECT: The Economic Impact of Rheumatic Heart (RHD) on the Health System of South Africa (Master's Candidate Mr Assegid Hellebo)

Your recent letter to the hospital refers.

You are granted permission to proceed with your research, which is valid until **30 July 2018**, subject to the approval of Professor N. Ntusi

Please note the following:

- a) Your research may not interfere with normal patient care.
- b) Hospital staff may not be asked to assist with the research.
- c) No additional costs to the hospital should be incurred i.e. Lab, consumables or stationary.
- d) **No patient folders may be removed from the premises or be inaccessible.**
- e) Please provide the research assistant/field worker with a copy of this letter as verification of approval.
- f) Confidentiality must be maintained at all times.
- g) Should you at any time require photographs of your subjects, please obtain the necessary indemnity forms from our Public Relations Office (E45 OMB or ext. 2187/2188).
- h) Should you require additional research time beyond the stipulated expiry date, please apply for an extension.
- i) Please discuss the study with the HOD before commencing.
- j) Please introduce yourself to the person in charge of an area before commencing.
- k) On completion of your research, please forward any recommendations/findings that can be beneficial to use to take further action that may inform redevelopment of future policy / review guidelines.
- l) **Kindly submit a copy of the publication or report to this office on completion of the research.**

I would like to wish you every success with the project.

Yours sincerely

DR BERNADETTE EICK
CHIEF OPERATIONAL OFFICER

Date: 1 November 2017

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