



**UNIVERSITY OF CAPE TOWN**  
IYUNIVESITHI YASEKAPA • UNIVERSITEIT VAN KAAPSTAD

***The effect of distance to health facility on the  
maintenance of INR therapeutic ranges in rheumatic  
heart disease patients from Cape Town***

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MPH dissertation supervised by Dr Mark Engel and Prof Bongani Mayosi submitted  
in partial fulfillment of the requirements for the award of the degree of  
MPH (Master of Public health)

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University of Cape Town

***Dei gratia***

**The effect of distance to health facility on the  
maintenance of INR therapeutic ranges in  
rheumatic heart disease patients  
from Cape Town**

University of Cape Town

## **Abstract**

The research undertaken for this MPH dissertation examines the effect of distance on the maintenance of INR therapeutic ranges in rheumatic heart disease patients in Cape Town.

**Part A** is the research protocol which outlines the background and the process of this research. This study is a population-based observational study nested within the Groote Schuur Hospital (GSH) cohort of a global study, REMEDY which is a prospective, multicentre, hospital-based registry for rheumatic heart disease (RHD). This study made use of geographical information systems (GIS) as a tool to investigate the effect of distance on the maintenance of INR therapeutic ranges in RHD patients.

**Part B** elaborates on the background and highlights the importance of this research by exploring the existing theoretical and empirical literature relevant to the topic. It describes the importance of the maintenance of the INR therapeutic range and how geographical factors can influence patient adherence to medication, and how it can act as a barrier to access health care. It provides examples of how GIS has been used to investigate the effect of distance on adherence in other studies. This literature review aimed to establish whether the maintenance of therapeutic ranges in RHD patients on anticoagulant therapy is correlated with the distance travelled from patient's residence to the clinic where INR monitoring takes place.

**Part C** presents the entire research project in a format suitable for journal submission. The background of this research project is summarised and the results are presented and discussed.

## Part A: Protocol

## PROTOCOL SUMMARY

**Title:** The effect of distance to health facility on the maintenance of INR therapeutic ranges in rheumatic heart disease patients from Cape Town

*Rheumatic heart disease (RHD) patients who have had valvular replacements or have been diagnosed with atrial fibrillation (AF) require anticoagulation therapy. Therapeutic anticoagulation is measured by the international normalised ratio (INR) on a monthly basis once therapeutic levels in individual patients have stabilised. Lack of concordance with monthly INR monitoring in RHD patients is considered to be a contributor to stroke and other complications. Various factors for non-concordance have been suggested including limited access to health care facilities.*

*We hypothesize that the maintenance of INR therapeutic ranges in RHD patients is correlated with the travel distance from the patient's residence to the health care facility to which they have been referred. The aim of this study is to utilize Geographical Information Systems (GIS), which enables the visual representation of data so as to establish patterns and trends, to develop a spatial display instrument, mapping the residential addresses of patients against their respective designated referral clinic, so as to investigate the effect of distance on the maintenance of INR therapeutic ranges in rheumatic heart disease patients.*

<b>Design:</b>	Population-based, Observational.
<b>Population:</b>	Hospital patients with echocardiography-confirmed RHD enrolled in the REMEDY study.
<b>Sites:</b>	The Cape Town Metropole, South Africa
<b>Study Duration:</b>	Duration of data collection & analysis: 3 months
<b>Instrument &amp; Methods:</b>	This thesis will use existing (12 month follow-up) data nested within Remedy, a register-based system for capturing RHD data amongst consenting Groote Schuur Hospital patients.

**Objectives:**

**Primary:**

In patients on anticoagulation therapy:

- To correlate the distance of RHD patients' residences from their designated referral clinic with the maintenance of INR levels

**Secondary:**

- To determine the distance from RHD patients' residence to the closest clinic
- To map the pattern of clinic utilization amongst RHD patients through the development of spatial display images
- To report the average INR levels among RHD patients
- To conduct subgroup analysis amongst patients who have had valvular replacements

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## Definition of Terms

ARF	Acute Rheumatic Fever
RHD	Rheumatic Heart Disease
GAS	Group A Streptococcus
GIS	Geographical Information System
CRF	Case Report Form
INR	International Normalized Ratio
PT	Prothrombin Time

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## 1. BACKGROUND TO THE RESEARCH

Rheumatic heart disease (RHD), a condition characterised by permanent damage to the heart valves, is a consequence of repeated episodes of acute rheumatic fever in patients with failed secondary prophylaxis (Nkomo, 2007). The developed world has experienced a decline in the prevalence of RHD through improved living conditions and the use of penicillin for the treatment of Group A streptococcal pharyngitis. On the other hand, developing countries which account for 80% of the world's population continue to experience high cases of RHD; RHD and its precursor, acute rheumatic fever (ARF) are the most common diseases affecting children and young adults in the world (Carapetis et al., 2005).

Primary and secondary prevention strategies to prevent disease progression, have been implemented in many parts of the world as per the World Health Organisation recommendations (WHO, 2004). Primary prevention specifically targets the correct management of GAS pharyngitis with penicillin, to avoid the later development of ARF (Robertson et al., 2005). If the first episode of ARF is not prevented, further episodes of ARF are prevented through the administration of a monthly prophylactic penicillin injection, known as secondary prevention (Manyemba and Mayosi, 2003). Worsening of valvular lesions in RHD patients can also be prevented through secondary prevention. .

Once damage to the valves have occurred, expensive heart valve surgery may be necessary failing which, the condition is usually fatal. Valvular repair or replacement with mechanical or biological prosthetic valves carries the risk of blood clot formation and embolism which may result in stroke (Salem et al. 2006). To prevent this complication, anticoagulant drugs such as warfarin are prescribed (Salem et al. 2006). Warfarin interferes with the vitamin K availability, thus prolonging the normal prothrombin time (PT) and preventing excess clotting (Hirsh et al. 2013). Anticoagulant levels in patients are monitored using the so-called International Normalized Ratio (INR). INR compares the clotting times in patients on anticoagulants with those of healthy

individuals and is represented as a ratio. Therapeutic levels representing normal values are between 2.00 – 3.00 for patients without valve replacements and 2.5 – 3.5 for patients with mechanical prosthetic valve replacements (Hirsh et al. 2013). Too high an INR value indicates a risk for abnormal bleeding, while too low a value indicates that the patient is not protected against clot formation. It is thus important to monitor patients' INR values on a regular basis so as to ensure that anticoagulant levels are maintained within the recommended ranges so as to ensure that therapies are effective in their function to reduce the risk of stroke and other complications in RHD patients.

## 2. Rationalé

The safety and effectiveness of anticoagulant therapy is crucially dependant on maintaining the INR within the therapeutic range (Hirsh et al. 2003). Anticoagulant treatment requires regular laboratory-guided adjustments of the dose as response to treatment is affected by interactions with food and drugs (Wallentin et al. 2010). Anticoagulation therapy with warfarin is highly effective at reducing the risk of stroke, but is associated with monitoring costs and a higher risk of haemorrhage compared with other treatments (Mant et al. 2007). The lack of concordance to monthly INR monitoring can thus cause complications such as stroke in RHD patients. Various factors for non-concordance have been suggested including limited access to health care facilities (figure 1).

Geographical factors such as distance from the patients' residence to their health care facility, so-called "Distance Decay", were shown to be a significant barrier to access (Gabrysch & Campbell 2009). It has also been shown that the usage of health services decreases as the distance to the patients' residence increases. (Målqvist et al. 2010).

The aim of this research is to evaluate distance as a factor in monitoring INR levels in RHD patients within the REMEDY cohort. Specifically, this study aims to investigate whether the distance of a patient's residence from their referral or

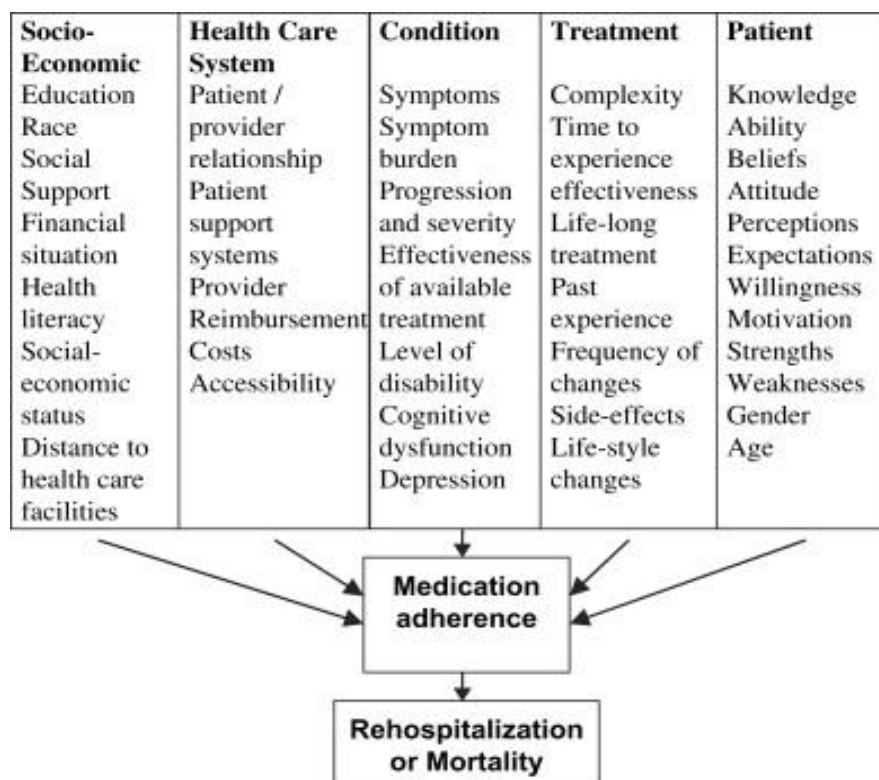


Figure 1: WHO's multidimensional adherence model and rehospitalization (Wu et al. 2008).

treatment clinic impacts on maintaining INR levels within the recommended therapeutic ranges over the scheduled monthly visits to the clinic. To date, the effect of distance decay on INR monitoring in patients' with RHD, has not been evaluated.

This work will develop a spatial display instrument for RHD cases to enable the mapping of patients' residential addresses and the referral clinic where they receive their monthly INR reading. Our results will inform healthcare providers where best to refer patients requiring monthly visits to clinics for INR monitoring. Furthermore, this work will inform the distribution of resources and personnel,

specifically taking into account patients' place of residence and areas where follow-up and concordance are lacking. Finally, it will also serve to highlight target clinics for awareness-raising interventions amongst patients, communities and healthcare practitioners.

### 3. Objectives

#### 3.1 Hypothesis:

INR measurement control is correlated with the distance from patients' residence to the community clinic to which they have been referred for anticoagulation therapy. We hypothesize that the rate of failure to maintain the INR therapeutic range increases as the distance between patients' residence and treatment clinic increases,

#### 3.2 Primary objective:

In patients on anticoagulation therapy:

- To correlate the distance of RHD patients' residences from their designated referral clinic with the maintenance of INR levels

#### 3.3 Secondary objective:

- To evaluate the distance from RHD patients' residences to the closest clinic
- To map the pattern of clinic utilization amongst RHD patients through the development of spatial display images
- To report the average INR levels among RHD patients
- To conduct subgroup analysis amongst patients who have had valvular replacements

## **4. METHODS**

### **4.1 Study Design**

This study is a population-based observational sub-study nested within the Groote Schuur cohort of a global RHD study, **REMEDY** which is a prospective, multicentre, hospital-based registry (Karthikeyan et al., 2011). The Remedy project aims to provide comprehensive, contemporary data on patients with RHD and will help in the development of strategies to prevent and manage RHD and its complications.

### **4.2 Recruitment and enrolment**

#### **4.2.1 Population**

Patients diagnosed with RHD and enrolled at Groote Schuur Hospital into the REMEDY study.

#### **Inclusion / exclusion criteria**

All patients recruited at the Cape Town REMEDY site for whom complete data are available for 12 month follow up and who reside in the Cape Metropole area.

#### **4.2.2 Method of sampling**

The sample will comprise a convenience sample of all the patients within the REMEDY database who satisfy the inclusion criteria.

### **4.3 Measurement**

This study will utilize Geographical Information Systems, better known by its acronym GIS, for capturing, manipulating, managing, analysing and displaying spatial and non-spatial data. The software has the ability to display various data sets on independent layers which is a key function to a successful GIS

system (Evans, 1997). In essence, GIS overlaps layers of information within a geographical area to give a better understanding from a composite viewpoint. The data in GIS is stored with geographical identifiers to enable for the data to be spatially located in the form of a map. Maps allow data sets to be viewed, understood, visualised and interpreted in many ways that reveal trends, patterns and relationships that could not be seen in two-dimensional tables or lists. GIS has been applied in a number of disciplines including civil engineering, geography and medical sciences.

#### **4.3.1 Data collection instruments and processes**

Patient data such as the diagnosis of ARF and RHD, residential addresses, assigned referral clinics and the latest three INR readings will be obtained from REMEDY patient records and captured into a purpose-designed database. In addition, government clinics across the metropole will be mapped using information supplied by the Department of Surveying and Mapping in Mowbray, Cape Town. All addresses will be converted to geographical coordinates and coordinates will be obtained from Google Earth<sup>®</sup>. The Geocoded addresses will be further checked in ArcGIS for errors in coordinate data. ArcGIS 10<sup>®</sup> software will be used for mapping and spatial analyses. The travel distance between individual residential addresses and referral clinics will be calculated and compared with the average of the latest three INR measurement readings of the patient. Additional outcomes include mapping the clinics to which patients are referred, versus the location of the nearest government clinic.

## Step 1:

The researcher will retrieve, from the patients' case report form (a collection instrument for demographic and diagnostic information) of the Remedy database, the following:

- physical residential address
- Clinic for referral
- Diagnosis
- Latest 3 INR measurement readings

Figure 2 below is an excerpt from the Case Report Form and the information that would be obtained from it.

The image shows a form titled "Registration" on "Page 2". At the top, there are three barcode-like fields labeled "DataFax #164", "Plate #002", and "Visit #001". Below these are "Subject ID" fields for "Centre#" and "Subject #", and "Subject Initials" with boxes for "F", "M", and "L". The "Subject's contact details" section includes: "a) Name:" with "Given name" and "Surname" fields; "b) Hospital #:" with a 10-digit box and the instruction "Please fill left to right"; "c) Home address:" with fields for "House No.", "Street", and "Postal/Zip Code/Box No.". Below these are fields for "Town/City", "Province/State", "Country", "GPS Coordinates", "Home #:", and "Work #:". At the bottom, there is a small text: "Application of GIS to Rheumatic Fever & Rheumatic Heart Disease".

Figure 2: Excerpt from Case Report Form

Step 2:

Google Earth®, a virtual globe, map and geographical information programme, will be used to establish the longitude and latitude coordinates for the physical address of the patients. Patients' residence on the street map provided is returned in decimal degrees.

Figure 3 below demonstrates how Google Earth will be used to establish coordinates for the various addresses of RHD patients.

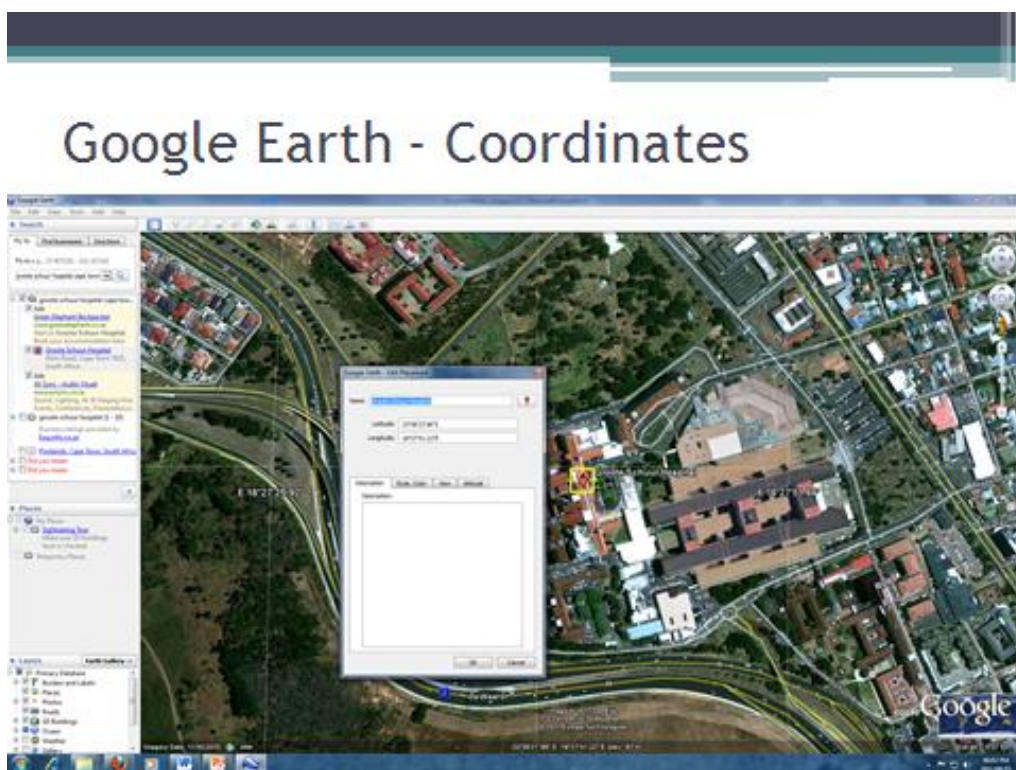


Figure 3: Google Earth - determining the co-ordinates

Step 3:

Google Maps® will be used to establish the closest road travel distance between the patients' residences and their treatment INR clinic using the coordinates obtained in step 2.

Figure 4 below displays how Google Maps will be used determine the shortest road travel distance between patients' residence and their treatment clinic.

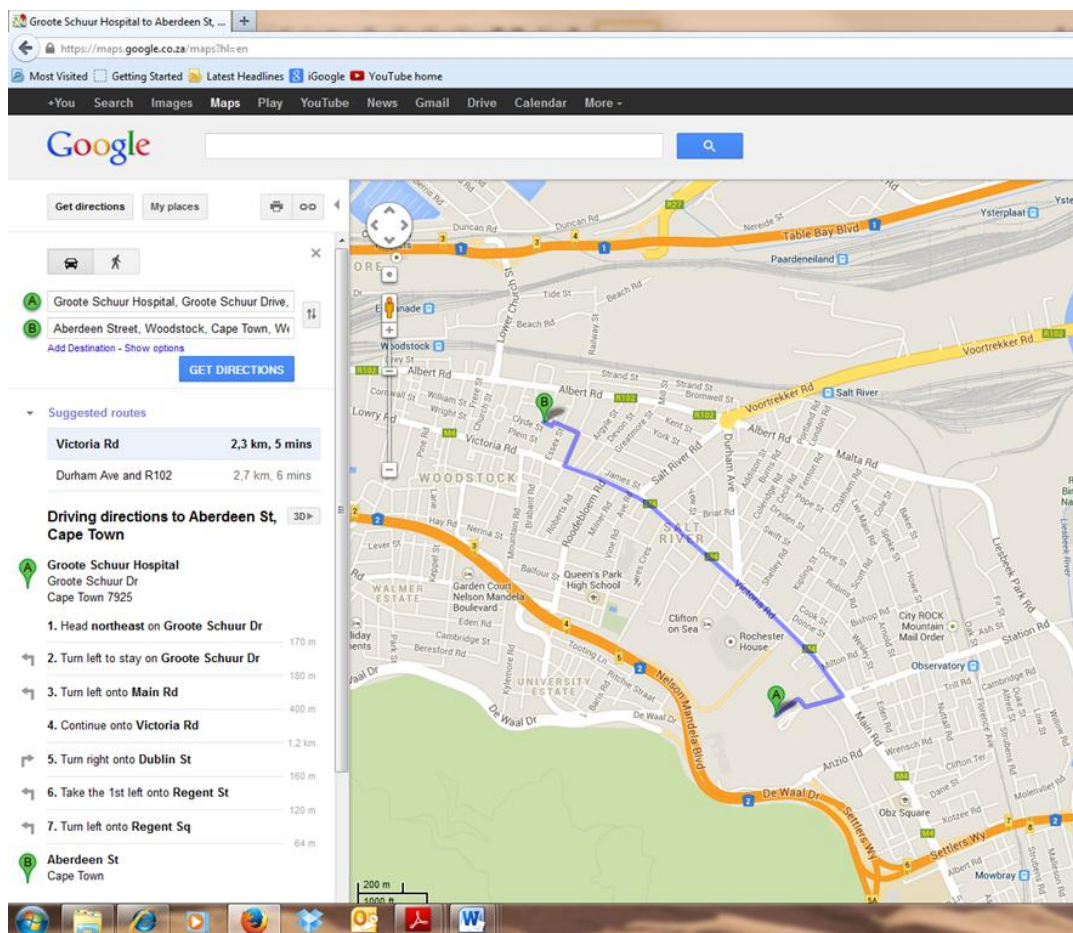


Figure 4: Google Maps – determining the shortest road travel distance

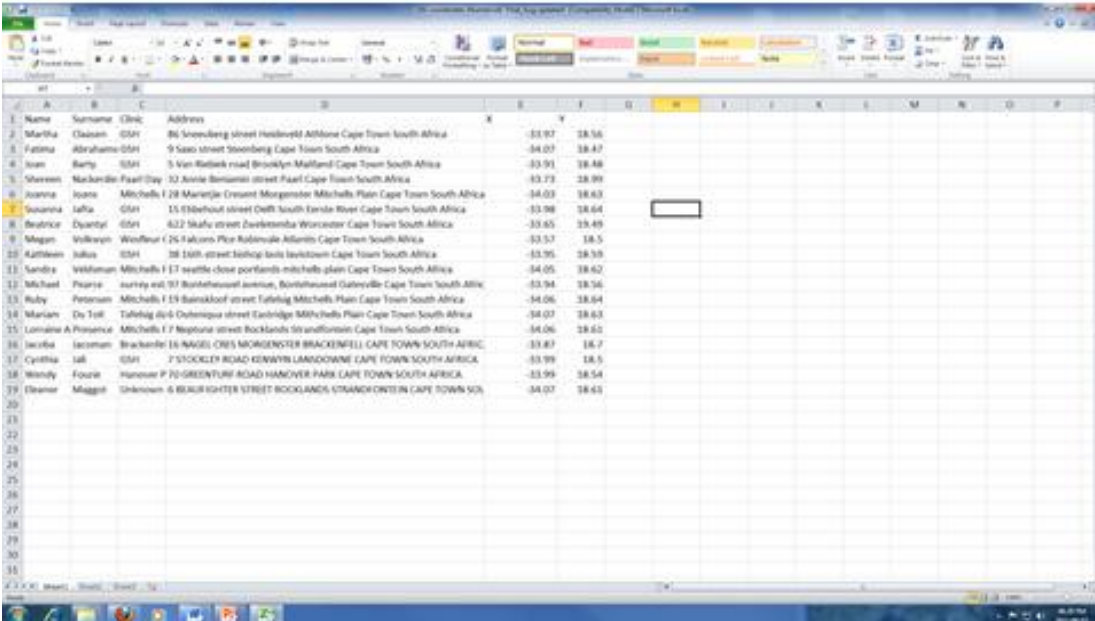
#### Step 4:

The data retrieved will be captured into a Microsoft Excel spreadsheet, together with the co-ordinates obtained from Google Earth. The coordinates are given in “decimal degrees” for input into the ArcGIS software.

Once the co-ordinates are presented in this format, the data are converted into a comma-delimited (CSV) file.

Refer to Figure 5 demonstrating the data in the spreadsheet together with the co-ordinates in the numerical system as required before the importing the .CSV file.

**Excel spreadsheet**



ID	Name	Surname	IDnr	Address	Latitude	Longitude
1	Marika	Clasen	0591	86 Snydersburg street Heidelberg Athlone Cape Town South Africa	-33.97	18.56
2	Fatima	Abraham	0591	9 Saso street Stoenberg Cape Town South Africa	-34.07	18.47
3	Joan	Barty	0591	3 Van Rielweg road Brooklyn-Mallard Cape Town South Africa	-33.91	18.48
4	Shereen	McKendrick	Paarl 0591	32 Annie Bismans street Paarl Cape Town South Africa	-33.73	18.99
5	Joanna	Joans	0591	12 Marietje Drenant Merganser Mitchells Plain Cape Town South Africa	-34.03	18.63
6	Suzanna	Jaffa	0591	15 Elsiehout street Delft South Eerste River Cape Town South Africa	-33.98	18.64
7	Beatrice	Djantyl	0591	422 Skafu street Zeebrenmba Worcester Cape Town South Africa	-33.65	19.49
8	Megan	Wolkyn	Wolkeur	125 F Alvens Pice Rabinsvale Atlantis Cape Town South Africa	-33.57	18.5
9	Luthean	Jullus	0591	38 16th street Isidip Isidip Isidip Cape Town South Africa	-33.95	18.59
10	Sandry	Wiltman	0591	17 Seattle close portlands mitchells plain Cape Town South Africa	-34.05	18.62
11	Michael	Papira	0591	107 Bonteheuwel avenue, Bonteheuwel Gatesville Cape Town South Africa	-33.94	18.56
12	Ruby	Petersen	0591	19 Bainskloof street Tafelberg Mitchells Plain Cape Town South Africa	-34.06	18.64
13	Marian	De Toll	0591	Tafelberg 41-6 Oudenburg street Cambridge Mitchells Plain Cape Town South Africa	-34.07	18.63
14	Lorraine A	Pronseca	0591	Mitchells 17 Neptunia street Bocklands Strandfontein Cape Town South Africa	-34.06	18.62
15	Jacoba	Secroman	0591	16 NAGEL CRES MORGENTHAU BRACKENFELI CAPE TOWN SOUTH AFRIC	-33.87	18.7
16	Cynthia	Jull	0591	7 SICKLETS ROAD KEMWYN LAMBOURNE CAPE TOWN SOUTH AFRICA	-33.99	18.5
17	Wendy	Equot	0591	70-GREENTURE ROAD HANOVER PARK CAPE TOWN SOUTH AFRICA	-33.99	18.54
18	Elleanor	Maggot	0591	6 BLAUW KANTER STREET BOCKLANDS STRANDfontein CAPE TOWN SOUTH AFRICA	-34.07	18.63

Figure 5: Excel database > \*.CSV file

### Step 5:

ArcGIS version 10<sup>®</sup> will be used to map and spatially analyse the data. The Comma-delimited CSV file will be imported into ArcMAP where the visual representation of the data will be displayed in the form of a 'picture'. Figure 6 is an illustration of the output which will eventually map the patients' residence as well as their referral clinic.

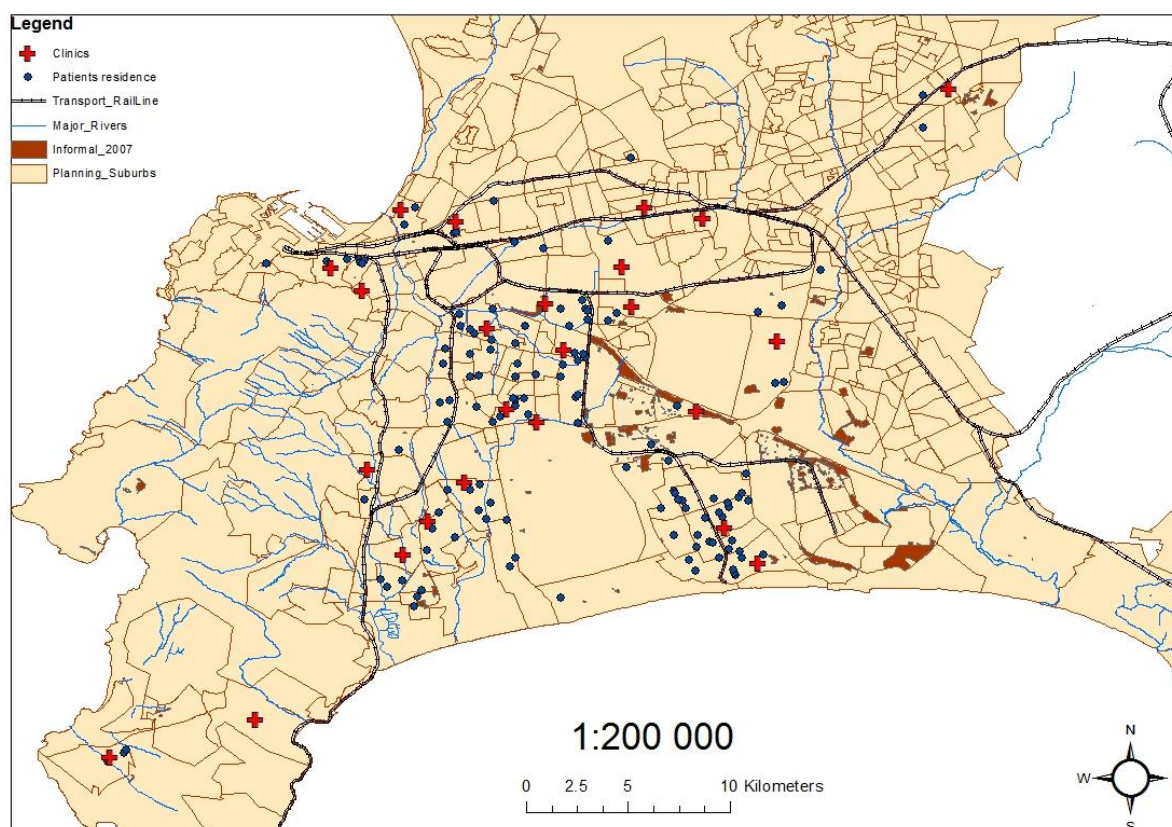


Figure 6: ArcMAP - Spatial representation of patients and clinics in the Cape Metropole

#### 4.3.2 Validity and reliability of measuring instruments.

While epidemiologists have traditionally used maps when analyzing associations between location, environment, and disease (Gesler, 1986), the application of GIS technology has been recently considered as an important

and new component in many epidemiological and health projects (Cromley, 2003). GIS technology aids the epidemiologist in understanding the subject under investigation to initiate interventions promptly. GIS presents statistical data in a spatially referenced manner through maps.

In particular, GIS enables the epidemiologist to:

- Determine geographic distributions of disease
- Observe surveillance and control infectious diseases
- Determine epidemics, monitor the growth and assists in the best approach with regard to intervention strategies
- Analyse spatial and temporal trends of disease, and
- Determine the population at risk by creating risk maps using the buffer tool in GIS.

GIS is particularly well suited for studying these associations because of its spatial analysis and display capabilities.

In a recent study conducted in Vietnam, GIS was used to investigate the effect of distance decay on delivery care utilisation (Målqvist et al. 2010). Distance decay is a term given to describe different settings and patient groups (Müller et al. 1998). The study examined the association between distance from a mothers' home to the closest health care facility as well as neonatal mortality. It then investigated the influence of distance on patterns of perinatal health care utilisation. The study found an increased risk of neonatal mortality among mothers living farthest away from a health facility.

In another study conducted in Baltimore County, Maryland, GIS and epidemiologic methods were combined to identify and locate environmental risk

factors associated with Lyme disease outbreak (Glass et al., 1995). Ecologic data such as watershed, land use, soil type, geology, and forest distribution were collected at the residences of Lyme disease patients and compared with data collected at a randomly selected set of addresses of unaffected individuals acting as controls. Data collected were layered within a GIS framework, generating spatial maps for a visual understanding of the extent of the epidemic. Finally, a risk model was generated combining both GIS and logistic regression analysis to locate areas where Lyme disease is most likely to occur.

In another study, also conducted in the USA, GIS was used in designing a national surveillance system for monitoring animal rabies cases. The system included data on positive and negative rabies cases as well as environmental information such as land use. The system provided a new resource for the rapid mapping and dissemination of data on animal rabies cases in relation to unaffected areas (Blanton et al. 2006) (Blanton et al., 2006).

GIS presents as an ideal tool with which to evaluate the effect of distance on INR monitoring of RHD patients.

## 5. DATA ANALYSIS

The data collected from the Remedy database for the purpose of this study as previously outlined, will be tabulated in an excel spreadsheet and analysed using STATA<sup>®</sup> version 11 and ArcGIS<sup>®</sup> version 10. The results will be stratified in terms of patients with and without valve replacements as their therapeutic INR range differs.

## 6. LOGISTICS

The researcher will commence with the research project June 2013 and is anticipated to last 3 months.

	June	July	August
Patient data extraction			
Data collation			
Analysis			
Write-up and compilation of final report			

This time period would allow the researcher to establish coordinates for all the patients in the Remedy database, investigate their concordance patterns to follow-up visits where they receive their monthly INR measurement readings and to compile maps of the data.

## **7. ETHICS**

This research thesis project is part of a larger research project that has already been approved by the HREC at UCT (028/2006). Specifically, this work will contribute to the analysis component of the registry, utilizing secondary data and will not involve any physical interaction with participants. Furthermore, there will be no direct benefits to the participants as a result of this study. All patient data used for the purpose of this research will be treated as confidential and anonymity will be maintained throughout the thesis and publication.

## **8. DISSEMINATION**

This research forms part of the dissertation for the Master of Public Health degree at the University of Cape Town. A copy of this dissertation will be made available at the Health Sciences library.

A manuscript describing the project and the results will be prepared according to the guidelines of a specific and appropriate peer reviewed journal and will be submitted for publication.

A scientific paper will also be prepared with the intent of an oral presentation at the Health GIS conference taking place in Bangkok, Thailand in August 2013.

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## Part B: Literature Review

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## 1. CLINICAL AND EPIDEMIOLOGICAL ASPECTS OF ARF/RHD

### 1.1 Pathogenesis

The mechanisms involved in the pathogenesis of Acute Rheumatic Fever (ARF) and Rheumatic Heart Disease (RHD) has been firmly established (Figure 1) (Guilherme & Kalil 2004)

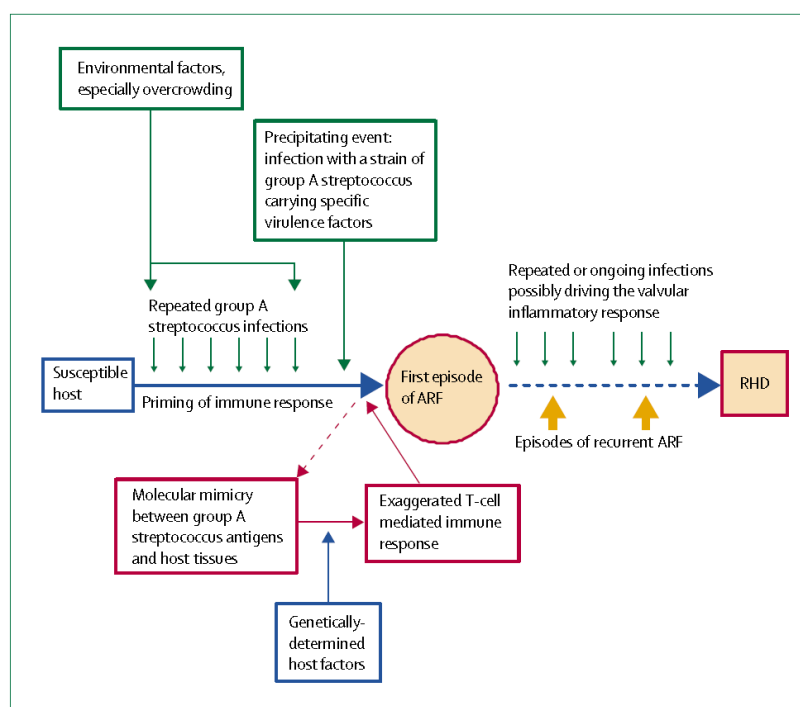
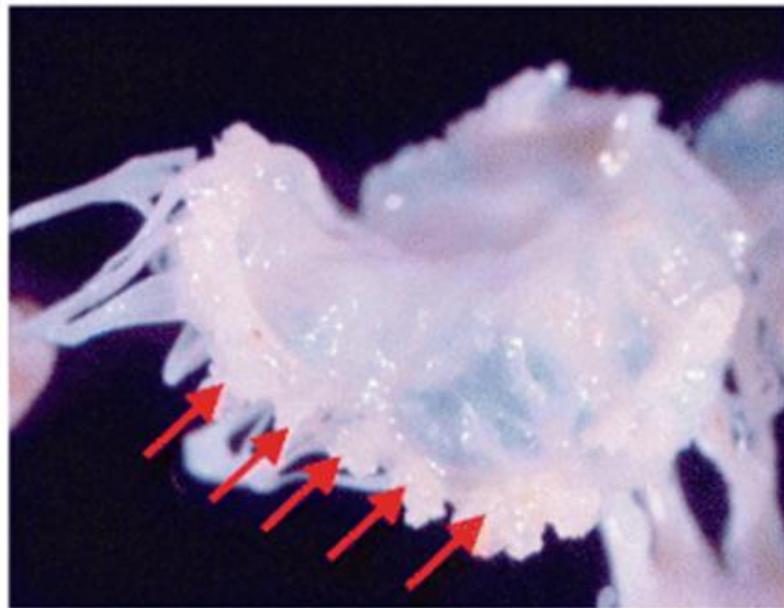


Figure 1: Pathogenetic pathways in ARF and RHD (Carapetis, McDonald, et al. 2005)

The initial event is a streptococcal pharyngitis (“Strep throat”) occurring in a susceptible host. Strep throat infection is particularly prevalent amongst the marginalised, often subject to poor environmental conditions, overcrowded communities, poor housing conditions, poor nutrition and inadequate health services (Carapetis, Andrew C Steer, et al. 2005) (A C Steer et al. 2002). Within 2 to 6 weeks, should the throat infection be left untreated, ARF may develop. ARF is an inflammatory disease which usually affects children between the ages of five and fourteen years (Carapetis, Andrew C Steer, et al. 2005).

It has been shown, at the immunological level, that the host antigens produced in response to the streptococcal infection in ARF patients, recognise the body's own structures as foreign thereby initiating an inappropriate response of self-destruction (auto-immune). This is due to the similarity of protein structures between the cell wall of the streptococcus bacteria and human joint tissue, brain tissues and heart valves, known as molecular mimicry (Guilherme et al. 2006). Thus, repeated episodes of infection exacerbate the destruction of the tissues, causing permanent heart valve damage known as Rheumatic Heart Disease (RHD). Briefly, GAS antibodies cross react with glycoproteins present in the heart valves, cardiac myosin and laminin. This facilitates CD4+ and CD8+ T cell infiltration in the valves resulting, in the case of the valves, the appearance of vegetations on the surface (figure 2) (Guilherme et al. 2007). More recently, a role for genetic susceptibility has been indicated in a recent study where it was shown that identical twins have a higher risk for concordance for ARF compared with non-identical twins (Engel et al. 2011).



*Figure 2: ARF surgical specimen of the mitral valve showing small vegetations on the line of closure (Guilherme et al. 2007).*

## 1.2 Clinical Manifestations of ARF and RHD

Arthritis is the most common major criterion for ARF, occurring in 80% of patients. The joints most commonly affected include the knee, ankle, wrist, elbow, hip and shoulder. The onset is sudden and associated with local signs of the inflammatory response i.e. swelling, tenderness, redness and hotness. The pain and swelling caused by arthritis is migratory and by the time the affected joint is healing, another large joint becomes affected (Alsaeid & Majeed 1998).

Carditis is the most important manifestation of ARF with an incidence of the carditis of 40–50% in ARF patients. In the acute stage, carditis can result in death or in severe morbidity caused by congestive heart failure. However, carditis can be subclinical and asymptomatic and detected only with colour Doppler echocardiography. (Reményi et al. 2012) (Marijon et al. 2012). Of note, carditis is the only sequel of ARF associated with long-term morbidity and of course mortality.

The mitral valve is most commonly affected in the initial attack, causing mitral valvulitis. The diagnostic clinical sign of mitral valvulitis (regurgitation) is the presence of a long, high pitched, blowing systolic murmur on auscultation. Valvular damage can only be detected by the use of echocardiography (Carapetis, McDonald, et al. 2005). The diagnostic clinic sign for aortic valvulitis (regurgitation) is the presence of the basal diastolic murmur. The murmur is short and begins immediately after the second heart sound (Alsaeid & Majeed 1998). In the acute phase, murmurs may also be due to endocarditis. Endocarditis may affect only the endocardium and can be detected by the presence of significant murmurs on auscultatory investigation.

ARF occurs around 3 weeks post the GAS infection (Meira et al. 2005). An inappropriate immune response to a GAS infection may initiate valvular damage. Even though the initial abnormal immune response may lead to severe valvular disease, RHD often results from reoccurring episodes of ARF which exacerbates valve damage (Carapetis, Andrew C Steer, et al. 2005). Clinical manifestations of chronic RHD include ventricular dysfunction and the development of aortic and mitral stenosis with various degrees of regurgitation.

### 1.3 Epidemiology of RHD

A decline in the prevalence and incidence of ARF/RHD has been observed in the developed world over the last 150 years, as a result of improved living conditions and the extensive use of penicillin, not only for the treatment of GAS pharyngitis (Carapetis, McDonald, et al. 2005). On the other hand, developing countries which make up 80% of the world's population continue to experience high cases of ARF/RHD. ARF/RHD is the most common acquired heart disease affecting children and young adults in the world (Carapetis, McDonald, et al. 2005).

ARF and RHD together, affects around 15.6 million people worldwide, 2.4 million of whom are children aged five to fourteen years old residing in developing countries. Furthermore, ARF/RHD leads to an estimated 350 000 deaths annually (Carapetis, Andrew C Steer, et al. 2005)(Carapetis, Steer et al. 2005). 0.3 – 3% of people progress to develop ARF if a streptococcus group A throat infection goes untreated. Approximately 40 – 60% of episodes of ARF results in RHD (Engel et al. 2009).

Figure 3 represents the global burden of RHD. It clearly demonstrates that Africa, which contains 10 % of the world's population, has a high share of people living with

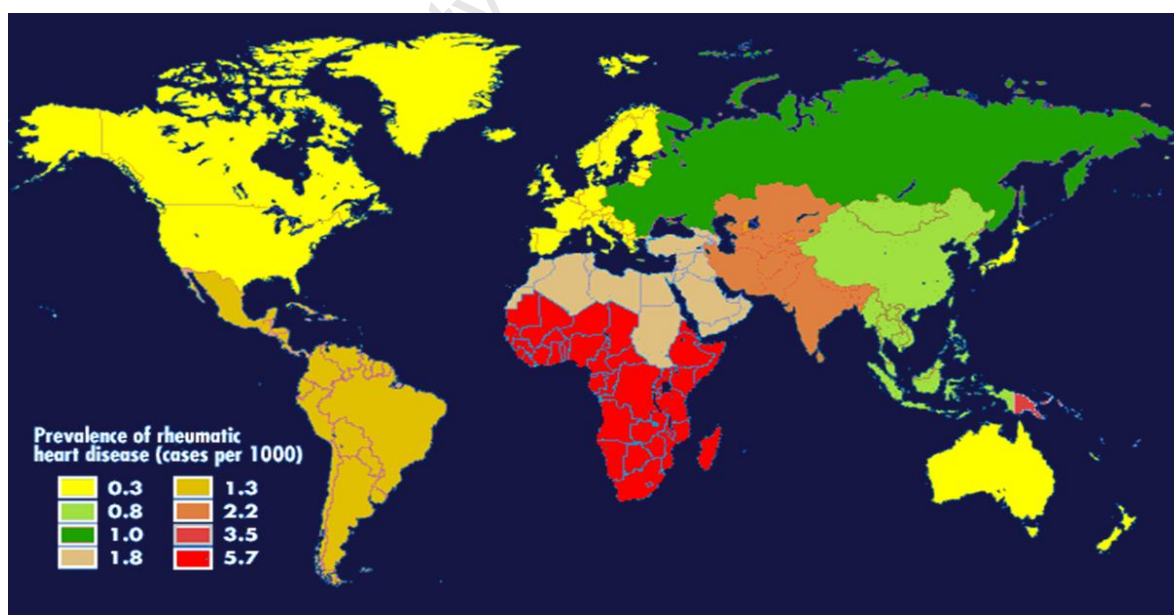


Figure 3: Map of the global burden of RHD (Carapetis, Andrew C Steer, et al. 2005).

RF/RHD. In 2002, half of the 2.4 million children living with RF/RHD reside in sub-Saharan Africa indicating that the disease is extremely prevalent here (Carapetis, Andrew C Steer, et al. 2005). Recent work from Seckeler et al. confirms the increase of RHD on the african continent (Figure 4) (Seckeler & Hoke 2011).

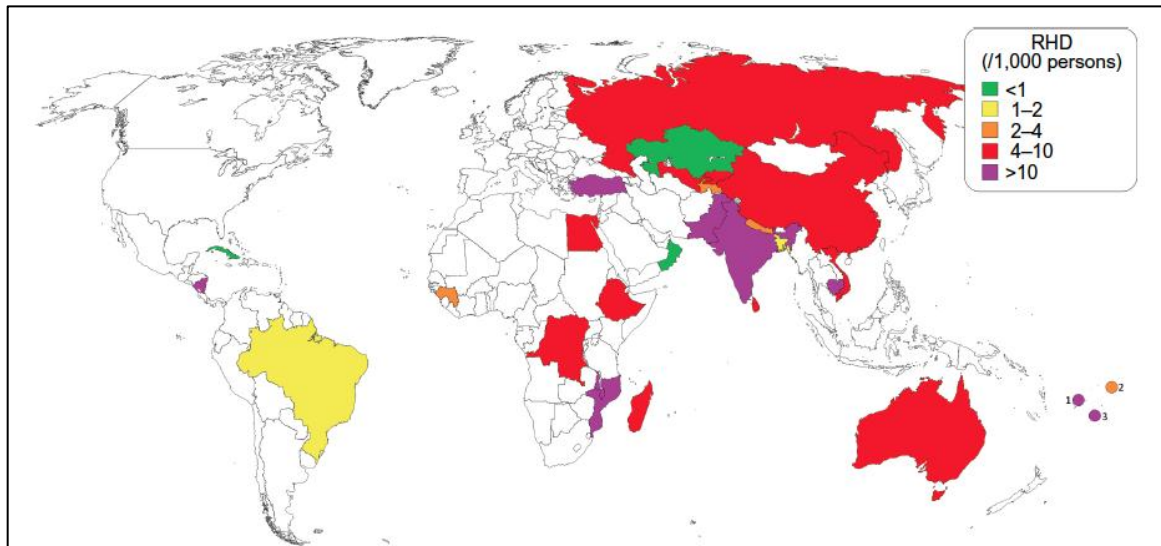


Figure 4. Map showing reported worldwide prevalence of RHD from 1991 through present (Seckeler & Hoke 2011).

Figures for South Africa are scant with the majority of studies having been reported before the advent of echocardiography. In a 2002 report from a paediatric cardiology conference hosted by the department of health, a consensus opinion was that South Africa was in the midst of an ARF epidemic despite national guidelines and recommendations for antibiotic prevention of the disease (Department of Health SA 2002). Furthermore, even though high numbers are being observed, there appears to be poor administration of the ARF notification system and underreporting of ARF cases by health care professionals in South Africa (Nkgudi et al. 2006).

## 2. PREVENTION

### 2.1 Primary and Secondary prevention

ARF and the development of RHD is almost entirely preventable using strategies that are cheap and cost effective. The World Health Organisation recognises ARF as being an illness of epidemic proportions and it being the most common cause of acquired heart disease affecting children in the world (World Health Organisation 2004).

The early detection, correct diagnosis and correct treatment of GAS pharyngitis with penicillin, prevents the first attack of ARF. This is referred to as primary prevention (Marijon et al. 2012). If the first episode of ARF is not prevented, further episodes of a GAS sore throat, which increases the chances of developing RHD needs to be avoided. This is known as secondary prevention (Manyemba & Mayosi 2003). Intramuscular long-acting penicillin is administered as prophylaxis to prevent further episodes of ARF and worsening of RHD. Table 1 details the WHO's guidelines for primary and secondary prevention strategies for the treatment of ARF/RHD. Table 2 defines the duration of secondary prevention relating to the severity of the carditis.

Table 1: WHO's guidelines for primary and secondary prevention of RF/RHD (World Health Organisation 2004).

<b>Antibiotic</b>	<b>Administration</b>	<b>Dose</b>
<b>Primary Prevention</b>		
<b>Benzathine benzylpenicillin</b>	Single intramuscular injection	1200000 units 600000 units <27kg
<b>Phenoxymethyl penicillin (Penicillin VK)</b>	Orally 2-4 times/day for 10 full days	Children: 250mg bid or tid. Adolescents or adults: 250mg tid or qid, or 500mg bid
<b>Amoxicillin</b>	Orally 2-3 times/day for 10 full days	25-50mg/kg/day in three doses. Total adult dose is 750-1500mg/day
<b>First-generation cephalosporins</b>	Orally 2-3 times/day for 10 full days	Varies with agent
<b>Erythromycin ethylsuccinate</b>	Orally 4 times/day for 10 full days	Varies with formulation. Available as the stearate, ethylsuccinate, estolate or base
<b>Secondary Prevention</b>		
<b>Penicillin</b>	Intramuscular injection. Every 4 weeks (28 days)	Children: < 20kg: 600 000 U Children >20kg or adults: 1,200 000U
<b>Penicillin VK</b>	Orally bd	250 mg bd
<b>Erythromycin</b>	Orally 2-4 divided doses per day	40mg/kg per day; 400mg adolescents and adults bd.

Table 2: Period of dose for secondary prevention (World Health Organisation 2004).

Category	Duration of prophylaxis
<b>All persons with ARF with no or mild carditis</b>	Minimum of 10 years after most recent episode or age 21
<b>All persons with ARF and moderate carditis</b>	Minimum of 10 years after most recent episode or age 30
<b>All persons with ARF and severe carditis</b>	Minimum 10 years after most recent episode or age 30 and then specialist review for need to continue. Post-surgical cases - life long

## 2.2 Tertiary Prevention

Once damage to the valves has occurred, valve surgery may be necessary to correct cardiac function (Marijon et al. 2012). This is warranted when patients become symptomatic as a result of severe valvular lesions (Bonow et al. 2006). Treatment options include valvular repair or replacement with either mechanical or biological (prosthetic) valves (Figure 5).

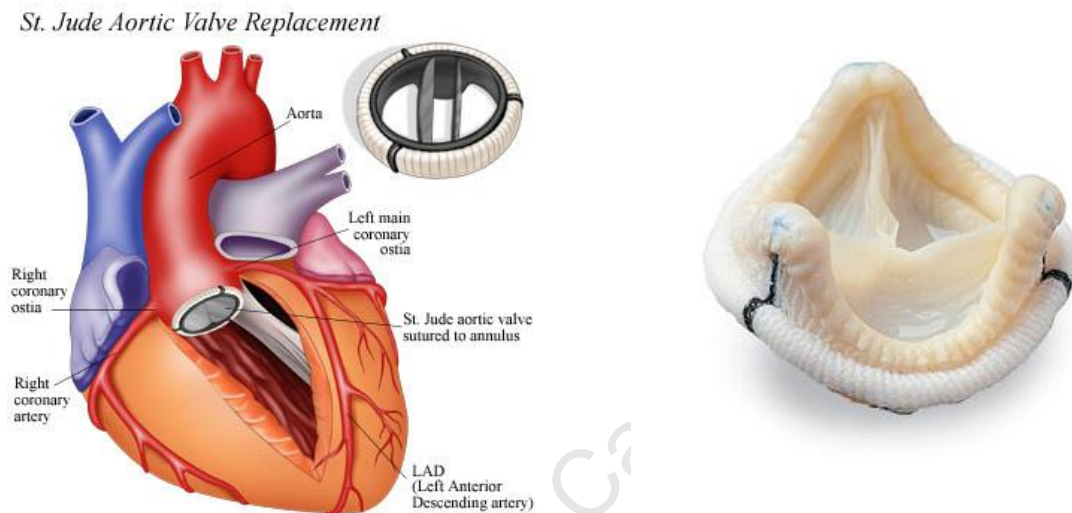


Figure 5: mechanical (left) and biological prosthetic valves (Advanced Practice Strategies n.d.) (Ostrovsky 2007)

Valvular replacement carries the risk of blood clot formation and / or embolism which may result in stroke (Salem et al. 2006). To prevent this complication, anticoagulant drugs such as warfarin are prescribed (Salem et al. 2006). Anticoagulants e.g. Warfarin, interfere with the availability of vitamin K, which plays a vital role in the natural clotting process of the body, and in doing so, prolongs the normal prothrombin time (PT) (Hirsh et al. 2013). The liver produces blood clotting proteins which are dependent on vitamin K to initiate the clotting process (Lefkowitz 2008) (Figure 6).

Anticoagulant levels are measured using the International Normalised Ratio (INR). It is important to monitor anticoagulant levels in patients, since they run the risk of

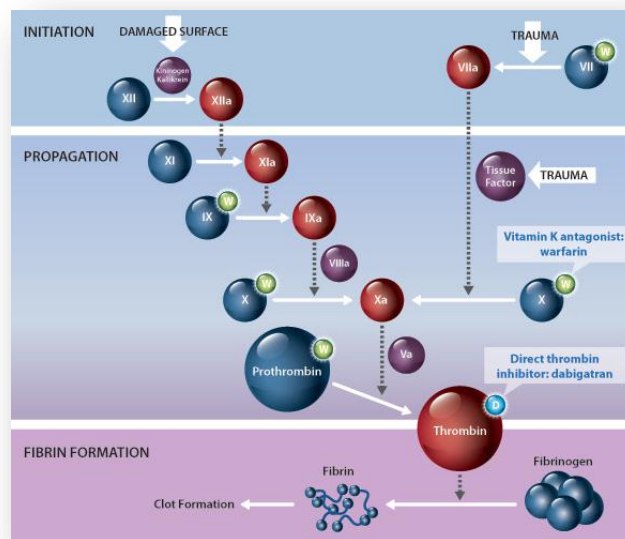


Figure 6: The clotting cascade (Anon 2011)

abnormal bleeding or excessive clot formation due to inadequate levels of anticoagulants of the blood. Maintenance of anticoagulant levels within the recommended therapeutic range ensures that therapies are effective in their function to reduce the risk of stroke and other complications in RHD patients (Kuruville & Gurk-Turner 2001).

Various factors for non-adherence to health-related interventions and monitoring have been suggested by the WHO, including distance decay (Figure 6) (Wu et al. 2008). Thus, it is imperative to identify those factors which serve as facilitators and barriers to adherence, in an attempt to reduce the risk of morbidity and mortality related to anticoagulation therapy.

### 3. LITERATURE REVIEW

#### 3.1 Aim of this study

The objective of this literature review is to establish whether the maintenance of therapeutic ranges in adult rheumatic heart disease patients, on anticoagulant therapy, is correlated with the distance travelled from their residence to the clinic where INR monitoring takes place.

#### 3.2 The study question.

*In adult rheumatic heart disease patients on anticoagulant therapy, is the maintenance of therapeutic ranges as measured by INR monitoring, influenced by road travel distance from patients' residence to their treatment clinic?*

#### 3.3 Literature search strategy

We searched the major databases including PubMed, ISI, and web of knowledge. We supplemented the search using Google scholar and by scanning reference lists of potential papers. Table 3 details the search strategy as used in the PubMed database together with the number of articles found; the search was modified accordingly for searching other databases.

Key words included

- INR,
- adherence,
- concordance,
- anticoagulation,
- anticoagulants,
- rheumatic heart disease,
- rheumatic fever,
- distance decay.

**Table 3: Details of search strategy indicating results from the PubMed database.\***

	SEARCH TERMS	PUBMED RESULT
1	RHEUMATIC HEART DISEASE	3195
2	RHEUMATIC FEVER	6261
3	#1 OR #2	8705
4	CONCORDAN*	38140
5	ADHEREN*	87190
6	#4 OR #5	124870
7	INR	5103
8	INTERNATIONAL NORMALISED RATIO	490
9	INTERNATIONAL NORMALIZED RATIO	3901
10	#7 OR #8 OR #9	6872
11	ANTICOAGULA*	60389
12	DISTANCE	138293
13	#3 AND #11	157
14	#3 AND #6	53
15	#12 AND #6	5
16	#12 AND #3	18
17	#12 AND #10	24

\* Other databases were searched with minor modifications according to the search engine requirements

### 3.4 Summary of literature

#### 3.4.1 Anticoagulant Monitoring: INR Ratio and Therapeutic Ranges

Therapeutic ranges are monitored using the so-called International Normalized Ratio (INR). The INR is a laboratory calculation which compares the clotting times in patients on anticoagulants with those of healthy individuals, represented as a ratio. Therapeutic levels representing normal values are between 2.00 – 3.00 for patients with biological prosthetic valves and 2.5 – 3.5 for patients with mechanical prosthetic valve replacements (Hirsh et al. 2013). Too high an INR value indicates a risk for abnormal bleeding, while too low a value indicates the patient is not protected against clot formation. It is thus important to monitor patients' INR values on a regular basis to ensure that anticoagulant levels are maintained within the recommended ranges so as to ensure that therapies are effective in their function to reduce the risk of stroke and other complications in RHD patients. Anticoagulant treatment requires regular laboratory-guided adjustments of the dose as response to treatment is affected by interactions with food and drugs (Wallentin et al. 2010).

The benefit of valve repair compared to replacement has been shown in many studies to be associated with favourable long-term outcome, reduced mortality rates and an improved quality of life in RHD children (Ciss et al. 2009). However, in instances where valve repair is not feasible, the option of prosthetic valve replacement is unavoidable. The choice for type of prosthesis is important and factors such as age, gender, geographical area, etc need to be considered in the context of likelihood of defaulting in adherence to anticoagulant treatment (Ferratini et al. 2013) (Marijon et al. 2012). Biological prosthesis in the mitral valve in young patients is prone to early deterioration, but on the other hand is associated with a lower incidence of thrombosis. A recent review concluded that in scenarios where the therapeutic range is successfully maintained in young people, mechanical prosthetic valve replacement should be preferred, even in young females who are now vulnerable to pregnancy risks (Ferratini et al. 2013).

### 3.4.2 Factors influencing INR maintenance within Therapeutic Ranges

The safety and effectiveness of anticoagulant therapy is crucially dependant on maintaining the INR within the therapeutic range (Hirsh et al. 2003). In RHD patients, the lack of concordance to monthly INR monitoring can result in complications such as stroke due to sub-therapeutic INR levels going unnoticed; in a cohort study evaluating the effect of warfarin on the risk of thromboembolism in 11,526 adult patients in atrial fibrillation of which 6,320 were in anticoagulant treatment, Go et al reported that during follow-up, there were 148 thromboembolic events, 141 of which were attributed to ischemic stroke among those on anticoagulant therapy. Lower rates of thromboembolism were observed amongst anticoagulant users with risk factors for stroke which included prior stroke, hypertension, diabetes, coronary heart disease and those 75 years and older (Go et al. 2013).

A number of factors for non-adherence / non-concordance as regards medication in general has been proposed, an explanation of which has been presented in the WHO's multidimensional adherence model, figure 7 (Wu et al. 2008).

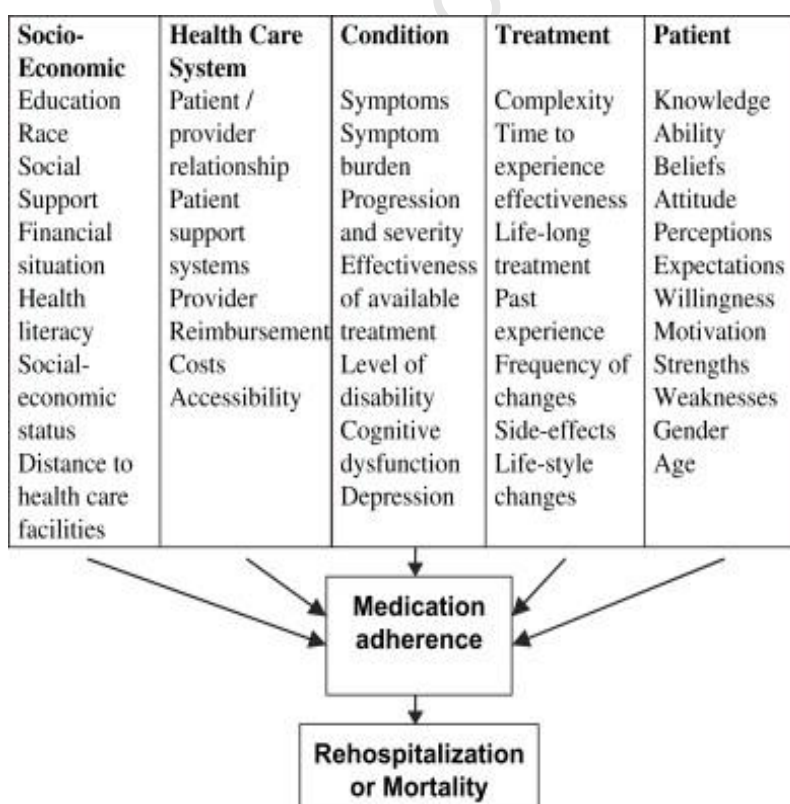


Figure 7: WHO's multidimensional adherence model and rehospitalization (Wu et al. 2008).

Briefly, the five broad categories which are described include socio-economic factors such as finance constraints, patient/provider relationship dynamics, the severity of the condition, the complexity of the treatment and also patient-related factors. Thus, it is imperative to identify those factors which serve as facilitators and barriers to adherence, in an attempt to reduce the risk of morbidity and mortality related to anticoagulation.

Medication adherence is largely attributed to the patient with only around 50 percent of information discussed with the patients at the time of consultation being recalled on a later occasion (Sabaté 2003)(Schillinger et al. 2013). Furthermore, patients with low literacy levels may be unable to read dosage instructions and information on a medicine bottle (Parikh et al. 1996).

It has been previously shown that poor adherence to anticoagulant therapy such as warfarin, is a major contributor to non-therapeutic anticoagulation (Cavallari et al. 2009) (Palareti et al. 2005). In a study conducted in Chicago in 2009, it was shown that patients who were provided with a monthly medication organiser improved warfarin adherence and significantly increased patients' length of time within INR therapeutic range (Nochowicz et al. 2009). Even though this intervention improved adherence, INR values still remained outside of the therapeutic range about 40 percent of the time. Thus the need for further studies are warranted to investigate additional interventions which could perhaps be used in combination with strategies that have already been shown to improve control and stabilise anticoagulation.

Many studies have examined various interventions to stabilise anticoagulation. One of such studies indicated how the use of computer software to track INR results and recommend changes in the dosage of anticoagulant treatment, as well as patient self-monitoring can be used to improve anticoagulation control and in so doing, reduce complications associated with INR measurements outside of the therapeutic range (Chiquette et al. 1998) (Beyth et al. 2000). These strategies are however, associated with considerable cost and are not feasible to implement in low-income settings.

### 3.4.3 Distance Decay as a factor for adherence

Geographical factors such as distance from the patients' residence to their health care facility (defined as "distance decay"), have been shown to be a significant barrier to access (Gabrysch & Campbell 2009). Briefly, as distance to reach services increase, the rate of service use decreases, resulting in a geographical health care disparity (Freehauf et al. 2013) (Müller et al. 1998).

### 3.4.4 Measuring distance decay using Geographical Information Systems (GIS)

While epidemiologists have traditionally used maps when analyzing associations between location, environment, and disease (Gesler 1986), the application of GIS technology has recently been considered as an important and new component in many epidemiological and health projects (Cromley 2003). GIS technology aids the epidemiologist in understanding the subject under investigation to initiate interventions promptly. GIS presents statistical data in a spatially referenced manner through maps.

In particular, GIS enables the epidemiologist to:

- Determine geographic distributions of disease
- Observe surveillance and control infectious diseases
- Determine epidemics, monitor the growth and assists in the best approach with regard to intervention strategies
- Analyse spatial and temporal trends of disease, and
- Determine the population at risk by creating risk maps using the buffer tool using the GIS.

GIS is particularly well suited for studying these associations because of its spatial analysis and display capabilities.

In a recent study conducted in Vietnam, GIS was used to investigate the effect of distance decay on delivery care utilisation (Målqvist et al. 2010). This study on neonatal mortality examined the association between distance from a mothers' home and the

nearest health care facility, specifically investigating the influence of distance on patterns of perinatal health care utilisation. It showed an increased risk of neonatal mortality among mothers living farthest away from a health facility. Similarly, another GIS-based study conducted in Kenya found that younger children and children with more severe illnesses travelled a further median distance to a health facility compared with older children with less serious illnesses; the rate of clinic visits decreased linearly at 0.5km intervals and stabilised after 4 kilometres (Feikin et al. 2009).

### **3.5 Summary and conclusions of the literature review.**

Maintenance of INR therapeutic ranges in adult patients on anticoagulant therapy is dependent on a number of factors, including adherence to anticoagulant therapy such as warfarin, which is influenced by geographical, socioeconomic and patient-related factors to name a few. Specifically, the distance travelled from patients' residence to the clinic where INR monitoring takes place (so called, *distance decay*) has been shown to be a barrier to patients' attendance at health care facilities.

Distance may play a significant role in adherence to INR monitoring requirements amongst RHD patients on anticoagulant therapy. This semi-structured systematic review of the literature revealed that no studies exist on the effect of distance decay on the maintenance of INR therapeutic ranges among RHD patients. Thus, primary studies to investigate this phenomenon is warranted.

The primary aim of this thesis therefore, was to evaluate the effect of distance on the maintenance of INR therapeutic ranges amongst adult RHD patients on anticoagulant therapy. It is anticipated that the results of this study will serve to inform programmes so as to improve the rate of patients adherence to regular INR monitoring activities.

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## Part C: Journal Manuscript

## **The effect of distance to health facility on the maintenance of INR therapeutic ranges in rheumatic heart disease patients from Cape Town**

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## ABSTRACT

**Background:** Lack of adherence to International normalised ratio (INR) monitoring in rheumatic heart disease (RHD) patients is a contributor to stroke and other complications. This population-based observational study investigated whether distance affects the maintenance of INR within therapeutic ranges in RHD patients.

**Methods:** Patient residential addresses and their attending clinics, together with laboratory INR results were extracted from the REMEDY RHD Registry database. Addresses were converted to geographical coordinates and verified in ArcGIS 10®. ArcGIS 10® and Google Maps® were used for spatial mapping and obtaining shortest road distances respectively.. The travel distance between individual residential addresses and referral clinics was compared to the average of three INR readings of patients and compared with therapeutic ranges recommended by guidelines.

**Results:** RHD patients (n=133) reside between 0.2 km and 50.8 km (median distance, 3.60 km) from one of 33 referral clinics. Patients who maintained their INR within recommended therapeutic levels travelled a shorter median distance to their designated INR clinic (in range = 3.50 km versus out of range = 3.75 km,  $p=0.78$ ). This trend was consistent within the mechanical valve replacement subset of patients (n=105) (3.50 km versus 3.90 km,  $p=0.81$ ) but contrasted with patients who had not had mechanical valve replacements (n=28) where the patients who maintained therapeutic levels travelled a further median distance to designated clinics (3.45 km versus 2.75 km,  $p=0.84$ ). These non-statistically significant trends were consistent when considering patients attending community-based clinics as a subset. Patients with mechanical valves were significantly less likely to be within their INR range (O.R., 0.32; 95% CI, 0.11; 0.86). Again, this observation was consistent amongst the community-based clinics. (O.R. 0.28; 95% CI, 0.08; 0.89); however, this significant association was not observed at any of the individual clinics.

**Conclusion:** Distance did not have an effect on the maintenance of INR within therapeutic range amongst RHD patients enrolled within our study in Cape Town.

KEY WORDS: GIS, INR, RHD, ARF, Adherence

## BACKGROUND

Rheumatic heart disease (RHD), a condition characterised by permanent damage to heart valves, is a consequence of repeated episodes of acute rheumatic fever (ARF) in patients with failed or non-existent secondary prophylaxis (Nkomo 2007). Over recent decades, industrialised countries have experienced a significant decline in the prevalence of RHD through improved living conditions and the use of penicillin for the treatment of Group A streptococcal pharyngitis, the initial event in the disease pathogenesis (Carapetis et al. 2005). In contrast, developing countries which account for 80% of the world's population, continue to experience high cases of RHD; RHD and its precursor, acute rheumatic fever (ARF) are the most common diseases affecting children and young adults in the world (Carapetis et al., 2005). Primary and secondary prevention strategies to prevent disease progression, have been implemented in many parts of the world as per the World Health Organisation (WHO) recommendations (World Health Organisation 2004). Primary prevention specifically targets the correct management of GAS pharyngitis with penicillin, to avoid the later development of ARF (Robertson et al. 2005). If the first episode of ARF is not prevented, further episodes of ARF are prevented through the administration of a monthly prophylactic penicillin injection (known as secondary prevention) (Manyemba & Mayosi 2003).

A small percentage of patients may become symptomatic as a result of severe valvular lesions (Bonow et al. 2006), warranting corrective heart valve surgery (Marijon et al. 2012). Treatment options include valvular repair or replacement with either mechanical or biological (prosthetic) valves. Valvular replacement however, carries the risk of blood clot formation and / or embolism, which may result in stroke (Salem et al. 2006). To prevent this complication, anticoagulant drugs such as warfarin are prescribed. Warfarin acts by interfering with the availability of vitamin K, which is essential to initiate the clotting process, thereby prolonging the normal prothrombin time (PT) and preventing excess clotting (Hirsh et al. 2013)) (Lefkowitz 2008). Anticoagulation therapy with warfarin is highly effective at reducing the risk of stroke, but is associated with monitoring costs and a higher risk of haemorrhage compared with other treatments (Mant et al. 2007).

Anticoagulant treatment requires regular laboratory-guided adjustments of the dose as response to treatment is affected by interactions with food and drugs (Wallentin et al. 2010). Monitoring is done through the so-called International Normalized Ratio (INR), which represents the comparison of clotting times in patients who have been prescribed anticoagulants against the clotting times in healthy individuals. Evidence-based clinical guidelines indicate INR therapeutic level ranges for patients, which are between 2.00 – 3.00 for patients without valve replacements and 2.5 – 3.5 for patients with mechanical prosthetic valve replacements (Hirsh et al. 2013). Too high an INR value indicates a risk for abnormal bleeding, while too low a value indicates that the patient is not protected against clot formation.

The safety and effectiveness of anticoagulant therapy is crucially dependent on maintaining the INR within the therapeutic range (Hirsh et al. 2003). In RHD patients, the lack of concordance to monthly INR monitoring can cause complications such as stroke; in a cohort study evaluating the effect of warfarin on the risk of thromboembolism in 11,526 adult patients in atrial fibrillation of which 6,320 were in anticoagulant treatment, Go et al reported that during follow-up, there were 148 thromboembolic events, 141 of which were attributed to ischemic stroke among those on anticoagulant therapy. Lower rates of thromboembolism were observed amongst anticoagulant users with risk factors for stroke which included prior stroke, hypertension, diabetes, coronary heart disease and those 75 years and older (Go et al. 2013). Various factors for non-adherence to health-related interventions and monitoring have been suggested by the WHO, including distance decay (Wu et al. 2008) (Gabrysch & Campbell 2009). Distance decay is a term given to describe a phenomena observed between two locations. As distance to reach services increase, so does the rate of service use decrease causing geographical health care disparities (Freehauf et al. 2013). A systematic review of the literature revealed that there exists no studies on the effect of distance decay on the maintenance of therapeutic ranges among RHD patients, thus supporting the need for primary studies to investigate this phenomenon.

In a recent study conducted in Vietnam, GIS was used to investigate the effect of distance decay on delivery care (Målqvist et al. 2010). The study found an increased risk of neonatal mortality among mothers living farthest away from a health facility.

Similarly, another GIS-based study conducted in Kenya found that younger children and children with more severe illnesses travelled a further median distance to a health facility compared with older children with less serious illnesses; the rate of clinic visits decreased linearly at 0.5km intervals and stabilised after 4 kilometres (Feikin et al. 2009).

The primary aim of this thesis was to evaluate the effect of distance on the maintenance of INR therapeutic ranges amongst RHD patients on anticoagulant therapy. Specifically, this study aims to investigate whether the distance of a patient's residence from their referral or treatment clinic impacts on maintaining INR levels within the recommended therapeutic ranges over the scheduled monthly visits to the clinic.

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## METHOD

### Study design

This was a population-based observational sub-study nested within the Groote Schuur Hospital cohort of the REMEDY study, a multicenter, prospective hospital-based RHD registry (Karthikeyan et al., 2011). The REMEDY project aims to provide comprehensive, contemporary data on patients with RHD so as to aid the development of strategies to prevent and manage RHD and its complications.

### Recruitment and enrolment

All Groote Schuur Hospital patients diagnosed with RHD and enrolled into the REMEDY study, were eligible to participate in the study. Patients were excluded if their data were incomplete at their 12-month follow-up visit, or if they resided outside of the Cape Metropole area which is located in the Western Cape province of South Africa. The Western Cape is divided into one metropolitan municipality (City of Cape Town) and five district municipalities.

### Data collection

Patient data including demographic details and residential addresses and clinical data such as diagnosis of RHD, INR readings and referral INR clinics were extracted from REMEDY patient records and captured into a purpose-designed database. Patient addresses were converted to geographical coordinates obtained from Google Earth<sup>®</sup>, while government clinics were mapped using information supplied by the Department of Surveying and Mapping in Mowbray, Cape Town.

### Geographical Information Systems

This study utilized Geographical Information System (GIS) software, ArcGIS 10<sup>®</sup>, for capturing, manipulating, managing, analysing and displaying spatial and non-spatial data. In brief, GIS overlaps layers of information within a geographical area to give a better understanding from a composite viewpoint (Evans, 1997). Information about geographical features (roads, boundaries etc.) was accessed from the ESRI database (<https://www.arcgis.com>). Data were projected in the Universal Transverse Mercator (UTM) system. The shortest road travel distances between homes and the health facility utilized by patients for INR monitoring were calculated using Google Maps and

entered into the study database (<https://maps.google.co.za/maps?hl=en>). Linear distances between the patients' home and closest health facility were calculated using the "near" function in the "proximity" toolbox in ArcMap 10<sup>®</sup>. The Geocoded addresses were checked in ArcGIS for errors in coordinate data. Distances mentioned are all one-way distances.

#### Data analyses

Statistical analyses and data handling were performed using STATA<sup>®</sup> version 11 and ArcGIS<sup>®</sup> version 10. INR readings were evaluated as a whole, and stratified according to valve replacements type, since bioprosthetic and mechanical valves differ with respect to INR therapeutic ranges. Pearson's chi-squared test and Mann-Whitney U test was used for group comparisons. A p-value of < 0.05 was considered significant. The road travel distance between individual residential addresses and referral clinics was compared with the average of the latest three INR measurement readings of the patient. Where appropriate, analyses were repeated excluding GSH hospital, given that it is the only tertiary hospital amongst the community-based clinics.

#### Ethical Approval

This research project was part of a larger research project that has already been approved by the Human Research Ethics Committee at the University of Cape Town (HREC 028/2006). This work contributed to the analysis component of the registry, utilizing secondary data and did not involve any physical interaction with participants.

## RESULTS

Of 500 patients enrolled at GSH in the REMEDY database, 133 patients met the inclusion criteria (i.e. patients who had complete INR data and, for whom full address details were available). Eighty-three percent of the cohort was female and 79% of patients (n=105) had had mechanical valve replacements. Co-morbidities included hypertension (27%), stroke (25%) and diabetes (19%) (Table 1). Of the 224 patients not meeting the inclusion criteria, 185 (83%) were female and 81 (36%) had had mechanical valve replacement, while the median age was 46 years (16 – 79).

Table 1: Baseline characteristics of participants

	N	%
GSH patients in REMEDY	500	
Patients with >12 month follow-up	357	
Patients with >12 month follow-up for whom data are available	<b>133</b>	
Average Age	53 years (+/- 1.25)	
Female	110	83%
Number of mechanical valve replacements	105	78.9%
<b>Comorbidities</b>	<b>n/N</b>	<b>%</b>
Hypertension	27/99	27%
Stroke	28/111	25%
Diabetes	19/98	19%

Figures 1 and 2 represent the spatial orientation of the RHD patients' residence and the INR clinics in the Cape Metropole region. INR monitoring was conducted among 33 clinics across the Cape Metropole. Road distances were not normally distributed; the median distance between the patient's residences and their respective clinics was

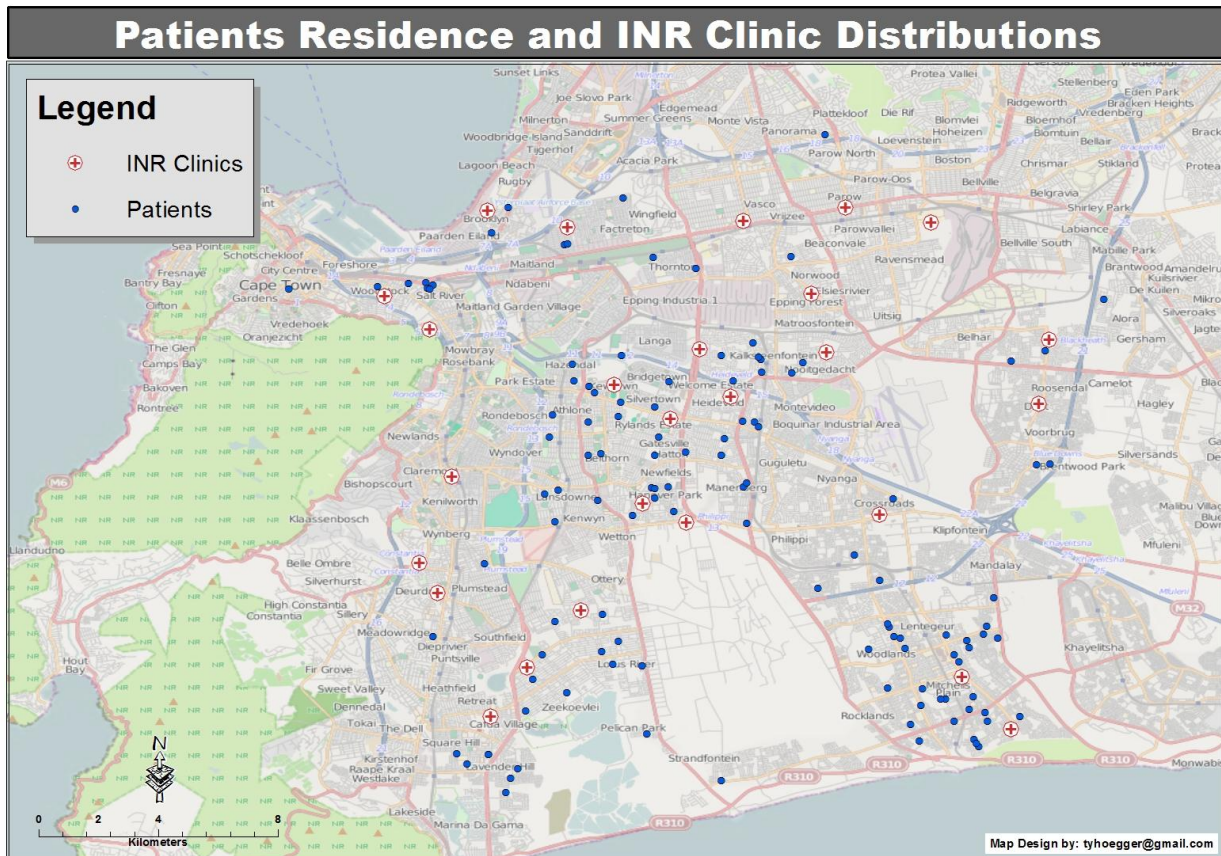


Figure 1: Map of the Cape Metropole showing patients residences and the clinics utilized for INR monitoring

3.60 km (range, 0.2km – 50.8km). Patients attending Groote Schuur Hospital (GSH), the only tertiary hospital included among the INR clinics, travelled a median distance of 18.2 km (1.6 km - 50.8 km).

Figure 2 displays the clinics utilized by RHD patients for INR monitoring as well as clinics not currently used for INR monitoring. The geographical distribution of these clinics indicate that patients could instead be utilizing clinics closer to their residences

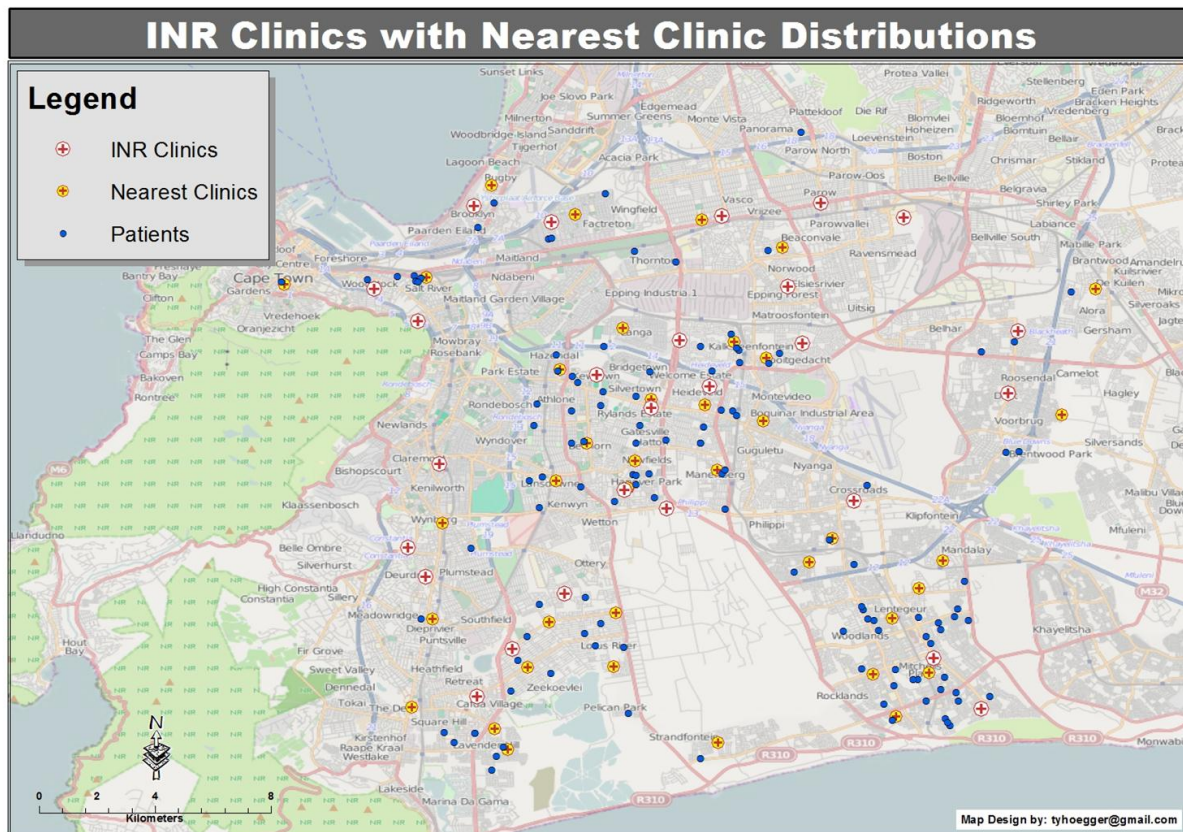


Figure 2: Map showing patients' residences, their designated INR clinic and the closest clinics

Table 2 details eight clinics utilized by 3 or more patients for INR monitoring, indicating the number of patients who maintained therapeutic levels according to whether or not they had had a mechanical valve replacement. Overall, patients with mechanical valves were significantly less likely to be within their INR range compared with patients who had no or bioprosthetic valve replacements (O.R., 0.32; 95% CI, 0.11; 0.86). This observation was consistent amongst the community-based clinics after excluding GSH (O.R. 0.28; 95% CI, 0.08; 0.89). However, this significant association was not observed at any of the individual clinics. Amongst all patients, irrespective of valve replacement or not, there was no difference in maintenance of INR within therapeutic range in patients from GSH versus those from community based clinics. (O.R., 1.44; 95% CI, 0.62; 3.41).

Table 2: Shortest median road distance from patients' home to health facilities

	Obs	No in INR range		Median KM
		MVR = No	MVR = Yes	
ALL CLINICS	133	20/28 (71)	47/105 (45)	3.60 (0.2 - 50.8)
‡ Excluding GSH	98	15/21 (71)	32/77 (42)	2.60 (0.2 – 27.3)
<b>Clinic Attended (&gt; 3 patients)</b>				
GSH	35	5/7 (71)	15/28 (54)	18.2 (1.6 - 50.8)
Dr Abdurahman CHC	10	-	3/10 (30)	2.95 (1.0 – 5.4)
Mitchell's Plain CHC	21	1/4 (25)	7/17 (41)	2.8 (1.2 - 5.6)
Heideveld CHC	10	1/2 (50)	3/8 (38)	2.75 (1.6 - 6.5)
Hanover Park CHC	8	1/1 (100)	4/7 (57)	1.1 (0.2 – 9.1)
Lady Michaelis	5	1/2 (50)	1/3 (33)	6.4 (1.8 – 14.0)
Woodstock CHC	4	1/2 (50)	1/2 (50)	1.55 (0.4 – 14.9)
<small>Obs, observations; No, number; KM, kilometers; MVR, mechanical valve replacement; GSH, Groote Schuur Hospital; CHC, community health clinic  ‡GSH is a tertiary facility and is not used for routine INR monitoring.</small>				

Among all the patients in our cohort, those who maintained their INR within recommended therapeutic levels travelled a shorter median distance to their designated INR clinic (3.50 km versus 3.75 km). (Table 3). However, this observation was not statistically significant ( $P=0.78$ ). This trend was also observed within the mechanical valve replacement subset of patients ( $n=105$ ) (in range = 3.50 km versus out of range = 3.90 km,  $p=0.81$ ). This trend however, contrasted with patients who had not had mechanical valve replacements ( $n=28$ ) where the patients who maintained therapeutic levels travelled a further median distance to their designated clinics (3.45 km versus 2.75 km,  $p=0.84$ ). This probably suggests that distance is not a factor in INR control.

Table 3: Median shortest road travel distance from patients' home to health facility, overall and by valve replacement type

	n (%)	Median KM
<b>All patients</b>		
Out of range	66 (49.6)	3.75 (0.4 - 50.8)
In range	67 (50.4)	3.50 (0.2 – 30.8)
<b>Total</b>	<b>133 (100)</b>	<b>P=0.78</b>
<b>Mechanical Valve = Yes</b>		
Out of range	58 (55)	3.90 (0.4 – 50.8)
In range	47 (45)	3.50 (0.2 – 30.8)
<b>Total</b>	<b>105 (100)</b>	<b>P=0.81</b>
<b>Mechanical valve = No</b>		
Out of range	8 (29)	2.75 (1.2 – 18.2)
In range	20 (71)	3.45 (1.0 – 24.0)
<b>Total</b>	<b>28 (100)</b>	<b>P=0.84</b>

Figure 3 depicts the distance of the closest clinic relative to the patient's home address: clinics are indicated by red crosses and the graduated dots represent the scale (based on size and colour ranging from yellow (0 – 0.5 km) to red (1.5 – 2.8 km) of the distance to the nearest clinic. The median distance from the patients' residence to the closest clinic is 0.67 km (0.08 – 2.80).

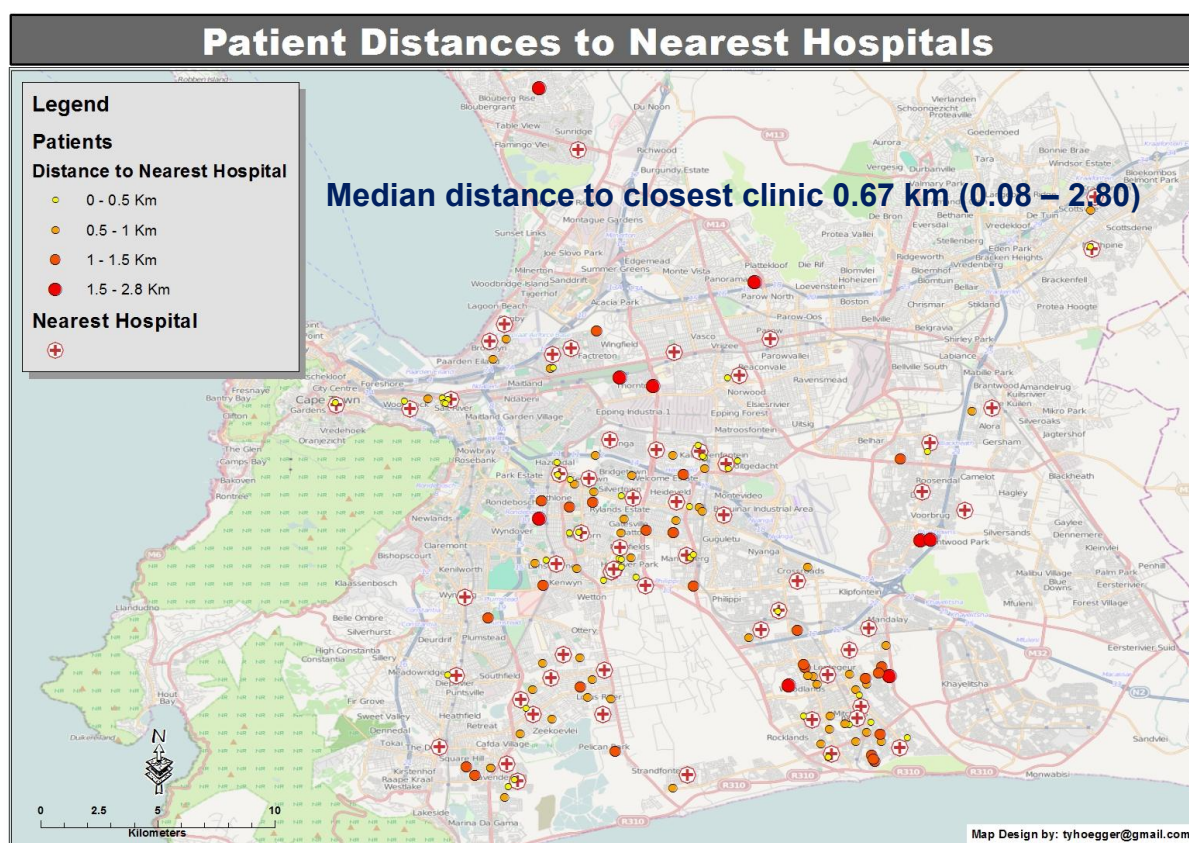


Figure 3: Map showing the distance to the closest clinic represented by the graduated symbols

Among those patients attending community-based clinics ( $n=98$ ), there was no difference in the median travel distance to their designated INR clinic between patients who maintained their INR therapeutic range and those who failed to maintain their therapeutic range ( $p=0.66$ ) (Table 4). Patients who have had mechanical valve replacements ( $n=77$ ) and who maintained their recommended INR therapeutic range, travelled a shorter median distance to their designated INR clinic (2.50km versus 2.90km); this observation was not statistically significant ( $p=0.47$ ). In contrast, patients who did not have mechanical valve replacements ( $n=21$ ) and maintained INR

therapeutic levels, tended to travel a further median distance (2.90km versus 1.90km) compared with those who failed to maintain therapeutic ranges; however, this finding did not reach significance (p=0.53).

Table 4: Shortest median road travel distance from patients' home to community-based clinics according to mechanical valve replacement status<sup>‡</sup>

	n (%)	Median KM
<b>All patients</b>		
Out of range	51 (52)	2.60 (0.4 – 27.3)
In range	47 (48)	2.60 (0.2 – 15.0)
<b>Total</b>	<b>98 (100)</b>	<b>P=0.66</b>
<b>Mechanical Valve = Yes</b>		
Out of range	45 (58)	2.90 (0.4 – 27.3)
In range	32 (42)	2.50 (0.2 – 15.0)
<b>Total</b>	<b>77 (100)</b>	<b>P=0.47</b>
<b>Mechanical valve = No</b>		
Out of range	6 (29)	1.9 (1.2 – 14.0)
In range	15 (71)	2.90 (1.0 – 11.4)
<b>Total</b>	<b>21 (100)</b>	<b>P=0.53</b>

<sup>‡</sup>Excludes GSH patients

## DISCUSSION

Out of pocket expenses has been identified as a barrier to adherence (Eaddy et al. 2012), thus longer travel distances implies more expenses. In this study, we examined the association between distance from an RHD patient's residence to their designated INR clinic, and the maintenance of INR within recommended therapeutic levels. There was no difference in the median distance between the residence of patients who maintained their INR readings within therapeutic range versus those who did not. (3.50 km versus 3.75 km;  $p=0.78$ ). Given that INR therapeutic ranges differ according to whether patients had undergone a mechanical valve replacement (MVR) or not (i.e. 2.0 – 3.0 for no or biological valve replacement, and 2.5 – 3.5 for mechanical valve replacement), we also considered MVR patients separately. There was a non-significant trend of INR therapeutic levels with travelling a shorter distance in MVR recipient patients ( $p=0.81$ ). By contrast, in non-MVR patients in good control travelled further distances than those out of control. These trends probably reflect a play of chance in a context in which distance did not play a role in INR control in Cape Town.

Participants for our study needed to have at least one INR reading, be within the geographical metropolitan area served by the hospital and have complete address information. In comparison to those excluded, gender and mean age were similar while the proportion of patients with mechanical valve replacements was noticeably different (79% vs 36% respectively). This may represent selection bias, and thus, a closer evaluation incorporating qualitative methods would be warranted in the future.

GSH is a tertiary hospital and the INR clinic deals particularly with patients who have been newly assigned to anticoagulant treatment. Thus, patients are more closely monitored during the initial phase while attempting to establish the correct dosing regimen; thus, results from GSH may bias our findings. Excluding the GSH patients ( $n=35$ ) and considering only those patients attending community-based clinics showed a trend that mechanical valvular replacement patients who maintained their INR therapeutic range travelled a shorter median distance compared with those who failed to maintain their therapeutic range. This observation was consistent amongst the MVR subset within this group; however the association was not statistically significant

in both instances ( $p=0.47$  and  $p=0.53$  respectively). The finding of non-MVR patients maintaining their INR ranges despite living further away was also seen in this group.

We made use of both linear and road distances in our analysis. The shortest road travel distances between patients' home and health facilities were measured using Google Maps®. To determine the median distance to the closest health facility from patients' residence, we made use of linear distance measurement. The median distance to the closest health facility was 0.67 kilometers (Straight-line distance), while the median road distance patients actually travelled to their treatment health facility was 3.60 kilometers. In our study, distance did not have an effect on the maintenance of INR control. Even though patients who maintained their INR therapeutic range travelled a shorter median distance compared with patients who failed to maintain their INR therapeutic range, this observation failed to reach statistical significance ( $P>0.05$ ).

Our results contrasts with studies which evaluated the effect of patients' travel distance on utilization of health services. A recent study on neonatal mortality conducted in Vietnam, showed an increased risk of neonatal mortality among mothers living farthest away from a health facility (Målqvist et al. 2010). In another, conducted in Kenya, it was found that younger children and children with more severe illnesses travelled a further median distance to a health facility compared with older children with less serious illnesses; the rate of clinic visits decreased linearly at 0.5km intervals and stabilised after 4 kilometres (Feikin et al. 2009).

One limitation of this study could be attributed to the sample size. Even though a trend was seen among patients who have had mechanical valve replacements, the association failed to reach statistical significance. Another limitation to this study could be attributed to the geographical measurement. Straight-line distances were used to calculate the distance to the nearest clinic from patient's residences. Moreover, another limitation may be the relatively short median distances travelled in Cape Town. It is possible that distance decay may be a factor in median distances of more than 50km's. Lastly, there are many factors which influence adherence. This study only managed to focus on distance, given the scope of the data in the registry. Information related to the mode of transport used to health facilities were not recorded,

however, most patients attending the public service use public transport. The informal taxi network is extensive and travel times per km are largely uniform.

The extent to which the straight-line distance measurement is used as a proxy for true distance is sometimes questionable. This raises concern when a particular geographical area of study has diverse features, for example, vast mountainous areas where there is limited road access. In this study, the geographical area has a good road infrastructure and is not affected by diverse geographical features. Furthermore, straight-line distances have previously been used in many studies including the Vietnam and Kenya studies discussed previously.

## CONCLUSION

Distance decay did not have an effect on maintenance of patients' INR therapeutic ranges. The median distance that patients in our cohort could be travelling however, is less than 1 kilometer suggesting that if patients attend a clinic within their residential area or a clinic nearest to their homes, it could reduce travelling time and out of pocket expenses associated with transport cost to access healthcare. . If patients utilize a clinic in their neighborhood or nearest to their residence, they could be reducing their expenses, which may improve adherence related issues. Furthermore, the load on already over-burdened clinics would be more appropriately spread.

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## *BMC Public Health* Manuscript Guidelines

[Criteria](#) | [Submission process](#) | [Preparing main manuscript text](#) | [Preparing illustrations and figures](#) | [Preparing tables](#) | [Preparing additional files](#) | [Style and language](#)

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- [Competing interests](#)
- [Authors' contributions](#)
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