A RETROSPECTIVE STUDY ON THE PROFILE OF PATIENTS ADMITTED WITH STROKE IN KLERKSDORP- TSHEPONG HOSPITAL COMPLEX AND THEIR CLINICAL OUTCOMES.

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A research report submitted to the faculty of Health Sciences, University of the Witwatersrand, in partial fulfilment of the requirements for the degree of Master of Medicine.

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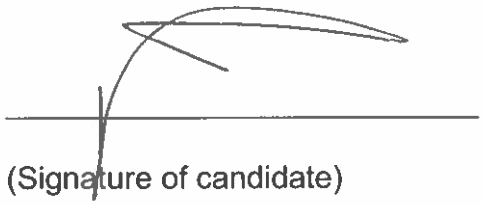
Declaration

I, Dr Palesa Mentoro declare that this research report (protocol with extended literature review and submissable article), being submitted for the Degree of Master of Medicine in the University of the Witwatersrand, is my own unaided work and has not been previously submitted for any other degree or examination at this or any other university.



(Signature of candidate)

18 day of JULY 20 22 at JOHANNESBURG

Dedication

To my family for their enormous support.

Abstract

Background: Cerebrovascular accident (CVA) is one of the leading causes of morbidity and mortality worldwide, with the majority being of an ischaemic nature and the minority are haemorrhagic. Increased age, metabolic and lifestyle diseases are the leading risk factors for this condition.

Objective: To describe the profile of patients admitted with stroke to Klerksdorp-Tshepong (KT) hospital complex, in the Northwest province of South Africa, and their management outcomes for the time period 01st January 2018 to 31st December 2018.

Methods: A retrospective analysis of the health records of patients admitted with CVA for the time period 01st January 2018 to 31st December 2018 in the KT hospital complex, Northwest Province. The following information was collected: demographics, co-morbidities, time of symptom occurrence and presentation to hospital, time to imaging, management, complications, and length of stay (LOS).

Results: The analysis included 121 patients of which 52.9% (n=64/121) were female, 55.4% (n=67/121) were over 60 years of age and 92.2% (n=106/115) were unemployed, half of the patients were referred from home (51.7%, n=60/116) and 63.0% (n=75/119) travelled an estimated distance of more than 10 km. Clinical manifestation noted were as follows: 83.5% (n=101/121) limb weakness, 36.4% (n=44/121) speech difficulty and 9.1% (n=11/121) facial weakness. Most patients utilised ambulance for transportation to hospital (59.5%, n=72/121). Many patients had an ischaemic stroke (89.5%, n=85/95), whereas 10.5% (n=10/95) had a haemorrhagic stroke. More than 90% of patients had co-morbidities (95.8%, n=115/120) which included: hypertension (74.8%, n=86/115), dyslipidaemia (30.4%, n=35/115), HIV (23.5%, n=27/115), diabetes (20.0%, n=23/115) and other (30.4%, n=35/115). The median time of onset of symptoms to CT scan was higher in patients with persistent disability than those who achieved neurological recovery (median time in hours [IQR]: 8.50 [5.0-12.0] vs. 6.0 [4.0-11.0]). Thrombolysis was received by only 1.7% (n=2/121). Overall in hospital complications were noted to be 10.1% (n=12/119). The discharge outcomes noted were as follows: persistent disability 67.8% (n=82/121), complete neurological recovery 22.3% (n=27/121) and death 9.1% (n=11/121).

Conclusion: Ischaemic stroke (IS) is the most common type of stroke seen in the study population, with a high number suffering persistent neurological impairment

associated with late presentation to the hospital. Only a minority access thrombolytic therapy. Health education on stroke is of paramount importance at community level (families, media, organisations, primary health care, emergency medical services etc.) regarding symptom recognition, early presentation to hospital as well as current management guidelines.

Key words: *Ischaemic stroke, stroke, cardiovascular disease, thrombolysis, Neurological impairment.*

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ABBREVIATIONS

A&E	Accident and Emergency
AHA	American Heart Association
APLS	Antiphospholipid syndrome
ART	Antiretroviral therapy
CAD	Coronary artery disease
CMV	Cytomegalovirus
CCM	Cryptococcal meningitis
CRF	Case Report Form
CT	Computerised Tomography
CTD	Connective Tissue Disease
CVA	Cerebrovascular Accident
DM	Diabetes Mellitus
EBV	Epstein Barr Virus
ECASS	European Cooperate Acute Stroke Study
HCW	Health Care Worker
HDL	High Density Lipoprotein
HIV	Human Immunodeficiency Virus
HPT	Hypertension
HSV	Herpes Simplex Virus
ICU	Intensive Care Unit
IS	Ischaemic Stroke
K/T	Klerksdorp/Tshepong
LDL	Low Density Lipoprotein
LOS	Length of Stay
NINDS	National Institute of Neurologic Disorder of Stroke
NW	Northwest
PI	Protease Inhibitor
SA	South Africa
SASS	South African Stroke Society
SASPI	South African Stroke Prevention Initiative
SLE	Systemic Lupus Erythematosus
TBM	Tuberculosis Meningitis

tPA	tissue Plasminogen Activator
VZV	Varicella Zoster Virus
WHO	World Health Organisation

CHAPTER 1: PROTOCOL WITH EXTENDED LITERATURE REVIEW

1. Introduction

1.1. Background

Cerebrovascular disease occurs mostly in the middle and late years of life. It is one of the leading causes of death globally due to neurological disability. It is the most common cause of mortality after coronary artery disease[1] and its incidence increases with age. Since 1990 the number of people affected by stroke has been increasing as well as those with resultant disability, and stroke related deaths[2]. In South Africa, stroke is responsible for an estimated 25 000 deaths annually[3]. It occurs commonly in people with Hypertension (HPT), Diabetes Mellitus (DM), Dyslipidaemia and smokers. HPT is the leading risk factor for stroke in South Africa; it is responsible for 1 in 2 (50%) strokes and 2 in 5 (40%) of heart attacks[4]. One in 4 adults have high total cholesterol (25%) and LDL cholesterol (25%) and 1 in 2 (50%) have low HDL cholesterol[5]. The burden of Human immunodeficiency virus (HIV) increases the risk of stroke in several ways including opportunistic infections, vasculopathy, cardio embolism and coagulopathy[6]. Use of antiretroviral therapy (ART) is beneficial, but can be atherogenic and could increase the risk of stroke[6]. HIV incidence is higher in the younger population[7] thus increasing the occurrence of stroke in young people[8].

Cerebrovascular accident manifests as a result of cerebral infarction or intracranial haemorrhage. It presents as a sudden onset of a focal neurological deficit. The deficit may be static, may improve or worsen with time. Control of modifiable diseases associated with stroke is the best prevention strategy. According to National Institute of Neurologic disorder of stroke (NINDS), those patients presenting early with an acute ischaemic stroke[9], thrombolysis has shown benefits in reversing disability, preserving life and maintaining activities of daily living.

Endovascular revascularisation is of growing interest in using thrombolytics via an intra-arterial route to increase concentration of drugs at the site of the clot and to minimise systemic bleeding complications within 6 hours of an acute stroke[10]. Also, of interest is thrombectomy in conjunction with thrombolytics in those patients without contraindications or thrombectomy alone, in patients presenting within 8 hours of stroke symptoms[10]. Surgical intervention in ischaemic stroke is not of common

practice in South Africa as compared to aneurysmal clipping in those with haemorrhagic stroke.

A review of medical records of patients admitted with a stroke from 01 January to 31 December 2018 was conducted to ascertain their profile, management and clinical outcome at the Klerksdorp/ Tshepong Hospital Complex. The hospital is part of the Angel's Initiative, an organisation that aims to increase global community of stroke centres and stroke-ready hospitals, to improve the quality of treatment for every stroke patient.

1.2. Definition of acute stroke

According to the World Health Organisation (WHO), stroke is defined by rapidly developing clinical signs of focal disorder of cerebral function; with symptoms enduring 24 hours or over and could lead to death, with no obvious cause other than of vascular origin. Symptoms and signs of stroke are determined by the vessel involved.

Anterior circulation stroke[11]

- Unilateral weakness
- Unilateral sensory loss or inattention
- Isolated dysarthria
- Dysphasia
- Vision- monocular blindness, homonymous hemianopia, visual inattention

Posterior circulation stroke[11]:

- Isolated homonymous hemianopia
- Diplopia and disconjugate eye movement
- Incoordination and unsteadiness
- Nausea and vomiting
- Unilateral or bilateral weakness and/or sensory loss

1.2.1. Types of stroke

A. Ischaemic stroke(IS)[10] - occurs from a blood clot or atherosclerotic plaque obstructing blood flow to the brain. This is commonly seen in those with atrial

fibrillation from various causes. Common site of atherosclerosis is seen at the aortic arch and the bifurcation of the common carotid arteries. Small atheromatous plaque may rupture and pass distally causing an obstruction to blood flow.

B. Haemorrhagic stroke [10] - An artery may rupture with bleeding into the brain parenchyma or into the space between the brain and meninges known as intracerebral and subarachnoid haemorrhage respectively. The most common cause of this type of stroke is an aneurysm. There are other rare causes such as an arterio-venous malformation.

C. Transient ischaemic attack (TIA) [12] - It is different from the other two types of stroke because blood flow to the brain is blocked only for a short time, usually no more than five minutes. Originally, TIA was defined based on the duration of neurological event. Recently a group of experts concluded to use a tissue based (not an arbitrary time based) definition of TIA which is primarily driven by modern imaging data, which discovered that as many as 50% of patients with momentary deficits lasting less than 24 hours have evidence of brain ischaemia on initial Magnetic Resonance Imaging (MRI) and 50% of those with initial abnormalities on MRI show substantiation of fixed infarction on follow up images.

D. Amaurosis fugax[10]- It is a type of TIA and often described as a curtain being pulled over the eye.

IS accounts for 85% of all strokes with haemorrhagic stroke occurring in about 15%[10].

1.2.2. Pathophysiology

The most common cause of IS is atherosclerosis, which causes damage to large vessels, with a preference for the aortic arch and its branches. The atherosclerotic plaque may dislodge to a distant area or cause local arterial injury with thrombus formation. Such stroke is called a thrombotic or embolic stroke. Stenosis of an extra- or intracranial vessel may produce a low-flow stroke or transient ischaemic attack in instances of reduced cardiac output or reduced systemic blood pressure.

In those with cardiac disease, atrial thrombi is the most common source of emboli. Such embolism is seen in cases of atrial fibrillation, myocardial infarction or valvular

heart disease, e.g. mitral stenosis. Hypercoagulable states can also result in ischaemic stroke commonly seen in anti-phospholipid syndrome (APLS) which may be associated with other autoimmune disease such as Systemic Lupus Erythematosis (SLE) or another rheumatic disorder[13].

In a haemorrhagic stroke, an artery ruptures causing blood to leak into the brain tissue resulting in cerebral oedema causing necrosis and tissue loss.

With the high prevalence of HIV, which is the leading cause of stroke in young patients, different mechanisms have been described as possible aetiologies to this, including opportunistic infections, cardio thromboembolism, coagulopathy and HIV associated vasculopathy[8]. Most commonly seen infections causing strokes are Tuberculous meningitis (TBM), Cryptococcal meningitis (CCM), toxoplasmosis, neurosyphilis, varicella zoster virus, Herpes simplex virus 1 (HSV-1), cytomegalovirus (CMV)[14]. In the presence of these infections, stroke occurs as a result of obliterative endarteritis and vasospasm. HIV infection may directly lead to HIV-associated vasculopathy via inflammatory mediators [14]. The term vasculopathy is defined as intimal hyperplasia more than expected for age, and thus involves several pathologic phenotypes of stroke found in HIV infection, including (1) HIV-associated accelerated atherosclerosis; (2) non-atherosclerotic vasculopathy (patients have non-vasculitic abnormalities, with intimal hyperplasia that can progress to stenosis or aneurysmal dilatation); (3) HIV-associated vasculitis and (4) small vessel disease[14].

SLE and APLS are seen commonly in females of reproductive age and may cause stroke through a vasculitic and thrombotic process respectively as a result of immune mediated vascular inflammation, antibody production against membrane phospholipid and their associated plasma proteins[13].

1.2.3. Complications

Following a stroke, patients may have limited mobility which predisposes them to pressure sores, muscle contractures and deep vein thrombosis. They may also have swallowing difficulties increasing the risk of aspiration pneumonia.

Stroke affects family dynamics as well. Patients may no longer be able to work or perform their previous roles in the family and they may become dependent on family to provide care. It also poses an economic burden due to the cost of medical care as well as loss of productivity resulting in loss of income[15]. According to a study conducted

in Nigeria, stroke patients have been found to be admitted between 7 and 14 days after initial symptoms, with longer length of stay (LOS) in older stroke patients and those with complications[16]. The Danish study of stroke survival rates have shown that patients who survived a stroke were five times more likely to die between four weeks and one year after their first stroke. The risk of death at 28 days after stroke, one year and five years were estimated to be 28%, 41% and 60% respectively[17].

1.2.4. Management

Most strokes occur at home or in the workplace[18] . To achieve the best outcomes, it is important that members of community and HCW (e.g. Primary health nurses, community healthcare workers, paramedics, Accident and Emergency personnel-A&E) recognise stroke as early as possible and initiate an emergency response and refer for appropriate management in a facility with a stroke unit.

According to the American Heart Association (AHA)[19] stroke is a medical emergency. The Stroke Unit Trialists'[20] collaboration done in 1990, which has been updated in the 2013 Cochrane review, found that patients with stroke who receive organised in-patient care in a stroke unit are more likely to be active, independent, and living at home, one year after a stroke.

The appropriate management of acute stroke described by South African Stroke Society (SASS) clinical guidelines involves the following key areas[21]:

a. Early recognition of symptoms using the Cincinnati prehospital stroke scale: FAST (**f**acial asymmetry, unilateral **a**rm weakness, **s**peech disturbances and **t**ime response) (Appendix A)
b. Early imaging with a non-contrast Computerised Tomography (CT) brain scan to exclude a haemorrhagic stroke within 30 minutes of hospital arrival.
c. Thrombolysis in those without contraindications should commence within 60 minutes of hospital arrival within 3 hours of neurological symptoms
d. Medical support in those not fulfilling criteria for thrombolysis.
e. Rehabilitation programme.

Over decades a large volume of research has been conducted in the study of thrombolysis and acute stroke.

The European Cooperative Acute Stroke Study I, II, III (ECASS)[22] tested intravenous recombinant tissue plasminogen activator for thrombolysis in acute stroke (intravenous tPA). In ECASS I high dose of 1,1 mg/kg, intravenous tPA was used in those with acute stroke presenting within 6 hours of neurologic symptoms. There was a high mortality rate as a result of intracerebral haemorrhage from thrombolysis. In ECASS II, a dose of 0,9 mg/kg was used for the same duration of symptom presentation, and this showed less intracerebral haemorrhage and less mortality. The low dose of 0,9 mg/kg of intravenous tPA was concluded to be safe. In ECASS III, a safe dose of fibrinolytic was studied in patients presenting within a shorter period of 3-4,5 hours of stroke symptoms and this showed no difference in outcomes and adverse effects in comparison to the National Institute of Neurological disorder and Stroke (NINDS). NINDS Trial 1 and NINDS Trial 2 observed the outcome of patients with acute stroke receiving 0,9 mg/kg intravenous tPA within 3 hours of onset had a better chance of functional independence with minimal or no disability 3 months after treatment.

Thrombolysis should be administered at a hospital with rapid triage of stroke patients and strict adherence to inclusion and exclusion criteria (Appendix B).

Despite great advances in acute stroke care, the desire for early intervention is still lacking. The study by Badachi S. et al.[23] identified that the hurdles to early hospital presentation are failure of patients to recognize a stroke (73%), lack of neuroimaging facility (58%), non-affordability (56%), failure of relatives to recognize stroke (38%), failure of primary care physician to recognize stroke (21%) and transport problems (13%). Also, awareness of thrombolysis as a treatment modality for stroke was found only in 2% of the population.

Post CT Brain, those with transient ischaemic attack should receive antiplatelet therapy immediately and urgent investigation because the risk of subsequent stroke is very high[24]. A large Chinese study indicated an early benefit in the prevention of vascular events with the use of a combination of antiplatelet therapy (aspirin plus clopidogrel) compared to aspirin monotherapy for an initial 3 month period after a TIA[25]. However, a recent systematic review did not find the combination to be superior to clopidogrel monotherapy once the diagnosis of TIA is confirmed[26].

Endovascular therapy has a longer therapeutic window of 6 and 8 hours with intra-arterial thrombolytic and thrombectomy respectively as compared to a 3 hours of intravenous thrombolytic. It is useful in achieving recanalization of blood vessels and improving functional independence. In addition, before intra-arterial thrombolysis can take place, two requirements will need to be met: arterial occlusion is proven and that the occlusion is reachable with interventional techniques.

1.2.5. Burden of disease

Maredza M. et al[27] studied the outcome of stroke in rural South Africa, in a sub-district of Bushbuckridge, Mpumalanga province. This study demonstrated that strokes are high in rural communities with a high mortality rate and an estimated 8.7% disability among stroke survivors. In another study, Maredza M. et al[28] found that an estimate of R2.5-4.2 million of Mpumalanga sub-district health expenditure was spent on the management of stroke, out of an estimated total health sub-district expenditure of R155 million. According to a study conducted for the period January 2014 to December 2018, from selected private and public hospitals nationwide, the estimated total direct cost were R7.3 trillion with R2.6 billion from inpatient care[29].

1.3. Methodology

1.3.1. Aim

Ischaemic stroke causes significant morbidity and mortality in low income countries and advancement in fibrinolytic therapy has shown clinical improvement in reversing disease, disability and death. The aim of the study was to ascertain a profile of patients admitted to KT hospital complex, their management and clinical outcome as it is a stroke ready hospital in the North-West province.

1.3.2. Study objectives

1. To evaluate the profile of patients presenting with stroke, i.e. age, gender, co-morbidities and type of stroke

2. To assess the time of presentation to hospital care and its appropriate management

- Time of onset of symptoms
- Time of arrival to hospital
- Time to CT-brain scan
- Time to thrombolysis

3. To assess the outcomes of stroke

- Thrombolysis outcome - complete or partial resolution and/ or failed thrombolysis or adverse event i.e. haemorrhage: intracerebral or systemic
- Deaths
- Outcome on discharge

4. To evaluate average length of stay

- Comparing those with and without complications such as thromboembolic disease, aspiration pneumonia, bed sore.

1.3.3. Study Design

This study was a retrospective cohort analysis of 121 patients who were admitted with a diagnosis of stroke at KT hospital complex within the period of 01 January 2018 to 31 December 2018. A patient registry from the medical admission ward 4 was used to identify patients. Folders were retrieved from archives as well as CTB scans and radiology reports.

1.3.4. Data Collection

Once permission was granted by the hospital to retrieve and use the file data, a request to retrieve patients' files was submitted to the records department and data retrieved from the files was transferred to a case report form (CRF), (Appendix C). Each patient was allocated a reference number and no names, surnames and national identification numbers were used, to maintain anonymity. Data collected included: demographics, presence of common risk factors i.e. Hypertension, Diabetes, Dyslipidaemia, smoking, HIV, TB and autoimmune disease. Time of arrival to emergency department, transport used i.e. private or ambulance, time of onset of symptoms and time of consultation, time to imaging and thrombolysis. With permission obtained from radiology department, CTB films in conjunction with radiology reports were reviewed including time of scan and diagnosis reported. The study categorised patients according to treatment received, i.e. conservative versus thrombolysis and surgery. Patients that were not treated with thrombolysis were assessed for contraindications to thrombolysis according to the South African Stroke Society guideline. Complications related to stroke, functional outcomes on discharge based

on resolution or established impairment, average length of stay and death were studied.

1.3.5. Statistical Analysis

Categorical data was analyzed and presented as frequencies and percentages together with the denominators overall and by gender, age group (<60 and 60+ years) and discharge outcomes (Persistent disability and complete neurological recovery or death) respectively. To test for statistical significance for categorical measures stratified by gender, age group and discharge outcome, Chi-Square test analysis or Fisher's test was used. Continuous measures were assessed using medians and inter-quartile ranges (IQR) as well as means and standard deviations and compared non-parametrically and parametrically using Kruskal-Wallis test and student t-test, respectively.

Time (in minutes) from symptoms of occurrence until CT scan and hospital arrival to CT scan were evaluated using Kaplan-Meier survival curves. The Kaplan-Meier log rank test was used to compare the differences in time between discharge outcomes. The curves were compared at 6 hours from symptoms occurrence until CT scans and 2 hours from hospital arrival to CT scan. All statistical analysis was conducted in SAS Enterprise Guide 7.1 using the procedures FREQ, MEANS, NPAR1WAY, TTEST and LIFETEST.

1.3.6. Ethics

Ethics approval was obtained from the Human Research Ethics Committee of the University of the Witwatersrand (Reference: M191198). Permission was also obtained from the management of KT hospital complex to conduct the research. Confidentiality of the patients was maintained throughout as all data collected remained anonymous and no patient identifier details were used in the study. Only the primary researcher had access to the data. Since this was a retrospective study, no harm was done to the patients.

1.4. Limitations

This was a retrospective study and the data obtained from the patients' records was dependent on the doctors attending to them during that period and may not have been accurate or complete at all times. There was also the issue of missing or misplaced patient records and files.

1.5. Study Timeline

	Research and protocol	Protocol submission	Data Collection	Data analysis	Research write-up	Study submission
January – September 2018						
October 2018– September 2019						
April 2020 – February 2021						
March – July 2021						
August 2021- March 2022						
April 2022						

1.6. Funding

The research expenses for this study were self-funded and included printing costs, stationery, and internet costs.

APPENDIX A

STROKE is an Emergency.

Every minute counts.

ACT F.A.S.T!

FACE Does one side of the face droop? Ask the person to smile.

ARMS Is one arm weak or numb? Ask the person to raise both arms. Does one arm drift downward?

SPEECH Is speech slurred? Ask the person to repeat a simple sentence. Is the sentence repeated correctly?

TIME If the person shows any of these symptoms, Call 911 or get to the hospital immediately.

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UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG	HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research & Post Graduate Affairs)

TO: Dr P Mentoro
School of Clinical Medicine
Department of Medicine
Division of Internal Medicine
Medical School
University

E-mail: 0402609N@students.wits.ac.za

CC: Supervisor: Professor B Luke <luke.binu@gmail.com>
and <HREC-Medical.ResearchOffice@wits.ac.za>

FROM: Iain Burns
Human Research Ethics Committee (Medical)
Tel: 011 717 1252

E-mail: Iain.Burns@wits.ac.za

DATE: 2020/03/18

REF: *R14/49*

PROTOCOL NO: **M191198** *(This is your ethics application study reference number. Please quote this reference number in all correspondence relating to this study)*

PROJECT TITLE: *A retrospective study on the profile of patients admitted with stroke in Klerksdorp - Tshepong Hospital Complex and their clinical outcomes*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to the Government funding of the University.

MSWorks2000/Iain0007/Clearscan.wps

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R14/49 Dr P Mentoro

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M191198

NAME: **(Principal Investigator)**	Dr P Mentoro
DEPARTMENT:	School of Clinical Medicine Department of Medicine Division of Internal Medicine Medical School University
PROJECT TITLE:	A retrospective study on the profile of patients admitted with stroke in Klerksdorp - Tshepong Hospital Complex and their clinical outcomes
DATE CONSIDERED:	2019/11/29
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Professor B Luke
APPROVED BY:	Dr CB Penny, Chairperson HREC (Medical)
DATE OF APPROVAL:	2020/03/18

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the 3rd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to submit details to the Committee. I **agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **November** and will therefore reports and re-certification will be due early in the month of **November** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

18/03/2022
Date

PLEASE QUOTE THE CLEARANCE CERTIFICATE NUMBER IN ALL ENQUIRIES