FACTORS ASSOCIATED WITH DIABETIC RETINOPATHY REQUIRING TREATMENT ON FUNDAL PHOTOGRAPHY IN PARTICIPANTS OF THE CAPE TOWN DIABETIC RETINOPATHY SCREENING PROGRAMME.

HENRY GEORGE ALEXANDER

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Supervisor: Prof Helen Schneider

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ness Prevention Diabetes

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Diabetic Retinopathy Screening

Fundal Photography

Risk Factors

ABSTRACT

BACKGROUND AND RATIONALE

The Cape Town Metro District Health Service (MDHS) has introduced a Diabetic Retinopathy Screening (DRS) programme incorporating retinal fundal photography in diabetic services at primary health care (PHC) facilities. Hitherto, coverage of the DRS programme has been less than optimal in part due to volumes of diabetic patients attending PHC facilities. The aim of this study was to identify possible sub-groups of patients, attending the Cape Town DRS Programme, who are at most risk of diabetic retinopathy and might be prioritised for early diabetic retinopathy detection and subsequent sight-saving treatment.

METHODOLOGY

A case-control study of risk factors for treatment-requiring diabetic retinopathy was conducted. This research sampled participants from the DRS programme provided by the MDHS eye care team to Type II diabetics attending public PHC facilities within the Klipfontein and Mitchells Plain Sub-Districts. Based on fundal images, cases were selected as those requiring ophthalmological treatment; and controls (three matched per case by area of residence) as those judged as not requiring ophthalmological treatment for diabetic retinopathy. Data on possible risk factors (clinical, laboratory) were extracted from the patients' folders.

RESULT

The study included 453 participants, of whom 113 (24.9%) were cases and 340 (75.1%) were controls. Three factors were significantly associated with treatment-requiring diabetic retinopathy on multivariate analysis: Insulin dependency (OR of 2.96, 95% CI: 1.75 – 5.00); duration of diabetes of more than 10 years (OR of 3.44, 95% CI: 2.06 – 5.74) and sustained hyperglycaemia over the past six months (OR of 3.73, 95% CI: 1.69 – 8.22). A screening algorithm combining these criteria had a sensitivity of 61.2% (95% CI: 51.9 – 70.5).

CONCLUSION

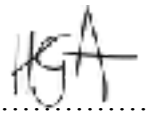
The findings indicate that a sub-set of patients attending the DRS programme in the Klipfontein and Mitchells Plain Sub-Districts have a greater likelihood of presenting with

treatment-requiring diabetic retinopathy. Further research is required to develop a tool that is sufficiently sensitive to safely prioritise patients for fundal screening.

DECLARATION

I declare that *Factors associated with diabetic retinopathy requiring treatment on fundal photography in participants of the Cape Town diabetic retinopathy screening programme* is my own work, that it has not been submitted for any degree or examination in any other university, and that all the sources I have used or quoted have been indicated and acknowledged by complete references.

Henry George Alexander October 2016

Signed 

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"We are all in the gutter, but some of us are gazing at the stars" Oscar Wild (1903).

CONTENTS

CHAPTER ONE: INTRODUCTION

BACKGROUND

It is predicted that by 2030 the global diabetic population will more than double from the 171 million people living with diabetes in 2000 (Bradshaw, Norman, Pieterse and Levitt, 2007). Sub-Saharan Africa will not be spared, and it is estimated that the diabetic population will increase by 80% from 10.4 million to 18.7 million by 2025 (Sambo, 2007). The prevalence of diabetes in South Africa is on the increase due to the cumulative effect of unhealthy lifestyle choices such as lack of exercise and poor nutrition. These lifestyle choices are promoted by prevailing socio-economic conditions e.g. poverty and urbanisation, and the policies which increase the import of low nutritional-value food products (Mash, 2010).

Diabetes mellitus, a complex chronic disease, demands extensive public health resources to prevent and treat the resultant plethora of complications (Mash, 2010). Diabetes impacts on both the macro- and micro-vascular systems leading to irreversible damage to these systems. Various studies have identified and described the risk factors associated with the incidence of diabetes such as obesity, smoking, and co-morbidities. However, there is little available information regarding risk factors and the onset and progression of diabetic retinopathy (Mash, 2010), although the general consensus is that the known risk factors for diabetes are also associated with the progression of diabetic retinopathy. The Early Treatment of Diabetic Retinopathy Study (ETDRS) is an example of a study where the risk factors for proliferative diabetic retinopathy were investigated (Davis *et al*., 1998). It identified elevated glycated haemoglobin (HbA1C) as a key risk factor.

Diabetic Retinopathy, a posterior ocular segment vascular disease which will affect 30% of all diabetics, is now the primary reason of blindness in the working age population. The shift in blindness attributed to posterior segment ocular disease has coincided with an aging population and the rise in non-communicable diseases (Cook and Qureshi, 2005). Diabetic retinopathy is largely asymptomatic in its early stage, which necessitates regular effective retinal screening. However only a small percentage of diabetics undergo diabetic retinal screening on a regular basis (Cook, 2013).

The increased prevalence of chronic disease in sub-Saharan Africa will necessitate the restructuring of primary health care to cater in the most efficient manner for the increased burdens, whilst also maintaining patients in good health as long as possible.

Chronic non- communicable disease care in South Africa is provided through a network of primary healthcare (PHC) facilities, which not only face a growing burden of non-communicable disease but also of communicable diseases and other health concerns, in what is known as a quadruple burden of disease (Mash, De Vries and Abdul, 2007).

The National Guideline for Prevention of Blindness in South Africa (an adaptation of WHO guidelines) offered some indication of policies to champion eye care services in South Africa (NDOH, 2002). However, the concurrent HIV/AIDS epidemic as well as other more pressing social and health issues has constrained the implementation of this policy. The release of the NHI White Paper brief has reaffirmed the importance of available eye care services at public primary health care service level, and emphasizes the positive economic impacts of good eye care (NDOH, 2015).

The main purpose of a Diabetic Retinal Screening (DRS) Programme is to prevent sight loss, as well as providing information on the overall systemic health of an individual. The advent of new technology such as non-mydriatic fundus cameras which allows for greater sensitivity, quantity and ease of use has made diabetic retinopathy screening viable; and enabled implementation of diabetic guidelines which require annual retinal screening.

As the prevalence rises, the services to prevent and treat diabetes will become increasingly stretched, making it difficult to screen diabetics on an annual basis for diabetic retinopathy. The purpose of this study is to provide the primary health care practitioner with an uncomplicated algorithm to assess a diabetic patient's risk of having treatment-requiring diabetic retinopathy, so that the patient may be prioritised for fundal photography and subsequently specialized treatment if need be.

RESEARCH SETTING

The City of Cape Town has an estimated population of 3.7 million of which approximately 80% is dependent upon the public health system for their health care needs. In Cape Town, the Metro District Health Services (MDHS) provide primary care to the uninsured population through a network of 45 Community Health Centres (CHC). It is currently estimated that 28,000 patients have been diagnosed with diabetes, and are receiving chronic care at the various primary health care facilities within the MDHS (Mash, Levitt, Steyn, Zwarenstein and Rollnick, 2012).

The study was conducted of the diabetic population who receive their anti-diabetic treatment at one of nine PHC facilities which fall within the geographical boundary of the Klipfontein and Mitchells Plain Sub-Districts, which are governed together as a "sub-structure" of the Cape Town Metropolitan District.

The Klipfontein and Mitchells Plain Sub-Districts, form part of what is known as the Cape Flatlands; an urban sprawl of majority low cost housing and informal settlements. The Cape Flatlands has a population of half a million, which has seen an increase of 27% over the last decade. More than two-thirds of the population resides in formal dwellings with the majority having access to the basic amenities i.e. sanitation, water and electricity. The sub-districts have an unemployment rate of 32%, and a low percentage (37%) of the population over the age of 20 have completed schooling (Stats SA, 2013). The Cape Flatlands has become synonymous with poverty, violence and despair.

PHC services within the Klipfontein and Mitchells Plain Sub-districts are provided through four and five day hospitals, respectively. These are predominately nurse driven services, and are the first point of service for the majority of people with chronic disease within the area. The Mitchells Plain District Hospital serves as a secondary care level referral hospital for the PHC facilities.

The Diabetic Retinal Screening (DRS) Programme hosted at primary health care level throughout the Cape Town Metro District Health Services (MDHS) uses a non-mydriatic camera (gold standard) to capture fundal images which are then graded, and further management recommended. This forms the primary point of case identification at public health care level of diabetic retinopathy (including secondary ocular pathology) with subsequent referral to tertiary care level for further management.

PROBLEM STATEMENT

The integration of eye care services into the comprehensive health care package provided at primary public health care level has not been adequately realised. The lack of available eye care services has been compounded by an increase in the demand for eye care services for diseases such as diabetic retinopathy, glaucoma and cataracts. The ever-increasing aging population as well as an increase in non-communicable disease has put added strain on eye care services.

As with screening programmes generally (Hofman, Cook and Levitt, 2014), diabetic retinal screening is only of value if it is integrated into a holistic care package that ensures adequate coverage through screening and with subsequent abnormal results acted upon. Monitoring systems often focus on the amount of diabetic retinal screenings conducted, neglecting quality and linkage to care aspects. In addition, where large volumes of patients are being screened, those most in need may not be identified or prioritised.

The MDHS is in the process of formulating a comprehensive eye care program, and one of the key areas for which evidence is required is how best to improve the detection and management of diabetic retinopathy (MDHS, 2011). Retinal Camera Imagery (RCI) currently provides the method for doing this, but given the large volumes of patients requiring screening, this study seeks to answer the question whether it is possible to identify patients most likely to have treatment-requiring retinopathy on clinical grounds. This should not undermine the present guidelines of annual retinal screening for all diabetics, but enhance the efficiency and effectiveness of the screening programme. Carmichael, Carp, Welsh and Kalk (2005) point out that within a context of resource scarcity, an effective and sustainable DRS protocol is of great importance if we are to successfully address avoidable blindness.

Laser photocoagulation is the primary treatment for diabetic retinopathy in South Africa, and the success and prognosis is dependent on the degree of diabetic retinopathy. The best outcome is produced by the early treatment of proliferative diabetic retinopathy and/or diabetic macular oedema, but the concern is that too many patients with diabetic retinopathy present at ophthalmology for treatment when the disease is advanced (Cook, 2013).

Identifying risk factors associated with treatment-requiring diabetic retinopathy may assist with the creation of an at risk diabetic retinopathy patient profile, which would enable better case detection.

AIM

The aim of this study was to identify sub-groups of Type II diabetic patients attending the Cape Town Diabetic Retinopathy Screening Programme who might benefit the most from, and should be prioritised for, early diabetic retinopathy detection and treatment.

OBJECTIVES

- To assess Type II diabetic patients who require laser treatment for diabetic retinopathy (cases) and those who do not require laser treatment (controls) based on fundal photography;
- To compare the risk profile of cases requiring laser treatment based on fundal photography to their matched controls;
- To identify risk factors, if any, associated with treatment requiring diabetic retinopathy;
- To propose a profile of patients most likely to require treatment, and to test the performance of simple algorithms to prioritise patients for fundal photography.

CHAPTER TWO: LITERATURE REVIEW

In this section I outline the international and national burden of diabetes, and the impact it has on the health system of a country. Diabetic retinopathy, a complication of diabetes and the main focus of this dissertation, will then be discussed and the available evidence on risk factors reviewed. The section will conclude with the identification of the knowledge gap surrounding diabetic retinopathy and its risk factors, and how this dissertation will attempt to address it, with the view to improving Diabetic Retinopathy Screening (DRS) in public primary health care settings.

DIABETES MELLITUS

The American Diabetes Association (1998:2180) defines diabetes as: "…a metabolic disorder primarily characterized by elevated blood glucose levels and by microvascular and cardiovascular complications that substantially increase the morbidity and mortality associated with the disease and reduce the quality of life". Diabetes is sub-divided into two Types: Type I Diabetes, constituting approximately 10% of the cases, who are wholly dependent on exogenous insulin due to the absolute lack of insulin production/secretion; and Type II Diabetes, representing 90% of all cases, characterized by a relative lack of insulin production and insulin resistance. Type II diabetes is further sub-classified into Insulin Dependent Diabetes Mellitus (IDDM) or Non-Insulin Dependent Diabetes Mellitus (NIDDM) (Innes, 2009). Diabetes is a complex disease for which the treatment and management demand significant health resources i.e. human, financial and equipment. The accessibility of these health resources is most often unequally distributed along a financial gradient, with poor people having fewer resources available to them (Landan & May, 2013).

GLOBAL DIABETIC BURDEN

Recent global statistics published by the World Health Organization (2016) indicate that there are 422 million people with diabetes worldwide, with a high proportion residing in developing countries. In 2014, diabetes resulted in 1.5 million deaths worldwide, with an additional 2.2 million deaths resulting from diabetes related cardiovascular complications.
Almost half of these deaths occurred prior to the age of seventy years, indicative of the high levels of premature deaths attributed to diabetes.

Africa bears the brunt of the global disease burden, with an increase in non-communicable disease over the past decade.

The Africa region's diabetic adult population is estimated at 14.2 million, with South Africa accounting for 2.3 million of these. The Africa Region also has the highest number of undiagnosed diabetics (International Diabetic Federation, 2015).

GLOBAL RESPONSE TO DIABETES AND OTHER NCDS

Chan (WHO, 2016) argues that the rapid increase in the diabetes prevalence in the last two decades is a sign of a shift towards increasingly obesogenic lifestyles, which have come as a result of a rise in urbanisation and changes in the food environment within developing countries. Prevention of Type II diabetes requires government action and global partnerships in the promotion of healthy food consumption and reduced production and promotion of poor quality food products (Mash, 2010).

The growing burden of diabetes is compounded by the ongoing high communicable disease burden. In South Africa, the concomitant ageing HIV-infected population is exacerbating the diabetic epidemic. The low availability of health care personnel in such a context makes it difficult to address this double burden with any lasting impact (Hofman, 2014). Davies and Mullan (2016) also argue that the lack of new research leaves us with little evidence on which to base our actions to address the double burden.

A number of global statements and processes seek to address the increase in diabetes prevalence. These include the United Nations General Assembly Outcome Documents on Non-Communicable Diseases and the Sustainable Development Goals (SDG) adopted in September 2015 (UN, 2015). These documents outline the importance of supportive governance, combined with the availability of affordable, accessible and sustainable health care, which includes preventative screening, availability of medicines and health promotion. They also recognise the intrinsic relationship between development and population health and the need for active trans-national participation in addressing diabetes.

The South African government has also initiated policies to pro-actively curb the incidence of diabetes and other NCDs, such as the recent sugar-tax, and smoking and salt regulations. These initiatives are imperative if one considers that complications from diabetes, stroke and coronary heart disease resulted in a cost of nearly $2 billion dollars in South Africa between 2005 and 2015 (Hofman, 2014).

EYE HEALTH AND DIABETES

Throughout Africa cataracts remain the leading cause of avoidable blindness, accounting for more than half of blindness (Lewallen and Courtright, 2001). In South Africa, cataracts and refractive errors are still the leading causes of blindness, and are being addressed through the roll out of the first phase of the "Vision 2020" initiative. However, with an ageing population diabetes, glaucoma and age-related macular degeneration (ARMD) are slowly gaining ground in the causes of blindness (Read and Cook, 2007). A recent study conducted in Cape Town which formed part of the Rapid Assessment of Avoidable Blindness (RAAB) programme, reflected a prevalence of blindness comparable to similar studies in other regions. Noticeably, a significantly higher proportion of those patients with severe visual loss had posterior segment disease. This indicates a gradual shift of avoidable visual loss away from cataracts towards posterior segment diseases (Cockburn *et al*., 2012).

Diabetic retinopathy is the leading cause of blindness in the adult population between 30 and 65 years of age in developed countries (Mollentze, 2003). This might be attributed to the greater access to services for other causes of blindness such as cataracts. In South Africa, diabetic retinopathy is the third leading cause of blindness with a reported prevalence of 20% amongst the diabetic population (Cook and Read, 2007).

Diabetic retinopathy is a micro-vascular disorder resulting in damage to the retinal vascular structure and is the primary ophthalmic condition associated with diabetes. It is associated with a multitude of other ocular conditions: cataract, glaucoma, and presbyopia, exacerbating the effects of retinopathy (IDF, 2015).

The high prevalence of diabetic retinopathy emphasizes the importance of routine retinal examination of diabetics at follow-up. This is seemingly a simple task, but the reality is that a low number of diabetics undergo regular annual retinal examination, due to lack of the necessary equipment combined with the lack of skills of the health personnel in performing some form of fundal examination e.g. ophthalmoscopy, retinal imagery or slit-lamp evaluation (Mollentze, 2003). Furthermore, the initial asymptomatic stage of diabetic retinopathy lulls the patient into a false sense of security exacerbated by their lack of knowledge pertaining to diabetic eye care. A study in Finland found that twenty percent of diabetics were not aware of the ocular complications associated with diabetes, and for those that knew that diabetes led to visual disturbance, the majority were not informed on how to prevent this (IDF, 2015).

Vision 2020, an initiative launched by the WHO in partnership with various custodians of eye care services globally, advocates the right to sight, and aims to eliminate avoidable blindness by the year 2020. Guidelines in accordance with Vision 2020 have been drafted by the South African National Department of Health, outlining various ocular disorders and strategies to address them (NDOH, 2002). However, the document does not provide guidance on translating these strategies into workable solutions at a primary care level.

SCREENING AND TREATMENT OF DIABETIC RETINOPATHY

Diabetic-related blindness can be prevented through implementing efficient retinal screening programmes and initiating early treatment procedures (Stefànsson *et al.*, 2000). Screening for, and treating diabetic retinopathy is considered to be the most cost-effective medical procedure known today (Hofman, Cook & Levitt, 2014). Cook (2013) has argued that retinal screening provides us with a state of the micro-vascular system which may provide insight into other co-morbidities, therefore making diabetic retinopathy screening (DRS) a vital public health investment. In countries where diabetic retinal screening has become part of routine public health care a drop in diabetic-related blindness has been achieved (Cook, 2014). However, even in developed countries with a comprehensive DRS programme, adherence to the guidelines of annual fundal photography of diabetics is still a challenge, with annual screening levels ranging from 34 to 65% of patients in various settings (Ciulla, Amador and Zinman, 2003).

Laser photocoagulation is the primary ophthalmic treatment for diabetic retinopathy. The success and prognosis is dependent on the degree of diabetic retinopathy. The best outcome is produced by the early treatment of proliferative diabetic retinopathy and/or diabetic macular oedema. However, the concern is that too many patients with diabetic retinopathy reach ophthalmological services for treatment when the disease is advanced (Cook, 2013).

Early intervention necessitates regular fundal examination of a diabetic by competent health personnel, preferably with the use of a non-mydriatic fundus camera which can clearly capture all four quadrants of the fundus, and creates a record for future comparison. Images are graded by degree of diabetic retinopathy and specifying the absence/presence of macular oedema, of which both guide the laser photocoagulation process (IDF, 2015).

The Early Treatment of Diabetic Retinopathy Study (ETDRS) developed the rules for treating non-proliferative diabetic retinopathy, known as 4-2-1 (IDF, 2015). Treatment is recommended when:

- micro-aneurysms are present in all four quadrants,
- venous beading is present in at least two quadrants
- intra-retinal microvascular anomalies are present.

The ETDRS has also indicated that these rules are not hard and fast and can be modified based on individual clinical assessments of risk and predictability of rate of progression of retinal changes.

Hofman *et al.* (2014) suggest that task-shifting may be appropriate for laser treatment, whereby an appropriately trained medical officer at secondary level will perform laser photocoagulation to reduce the burden of over-referral at tertiary care level raised as a possible stumbling block with the initiation of wide-spread diabetic retinal screening (Cook, 2013). Furthermore, this will allow better coordination between secondary and primary level diabetic eye care e.g. better communication, referral and sustained follow up.

RISK FACTORS FOR DIABETIC RETINOPATHY

Multiple studies have identified and described the risk factors associated with the incidence of diabetes (Mash, 2010). Fewer studies have specifically investigated the factors associated with the onset and progression of diabetic retinopathy.

The Early Treatment Diabetic Retinopathy Study (ETDRS) conducted in the United States of America is considered the most significant study of diabetic retinopathy to date. It identified the following factors for high-risk proliferative diabetic retinopathy: age, type and duration of diabetes, HbA1c levels and history of diabetic neuropathy (Davis *et al*., 1998).

The Hoorn study conducted in the Netherlands found chronic hyperglycaemia, hypertension and abdominal obesity to be significantly associated with incident diabetic retinopathy. In contrast, age, sex, Body Mass Index (BMI) and smoking were not significantly associated with incident diabetic retinopathy. Studies of the association between diabetic retinopathy and BMI, an indication of obesity, which in-turn is associated with insulin resistance, have not delivered any conclusive results. However, waist-hip ratio, an indicator of central obesity, has been identified as a risk factor for diabetic retinopathy in the EURODIAB Prospective Complications Study (Van Leiden *et al.,* 2003).

Metabolic abnormalities associated with diabetes such as hyperglycaemia, hypertension and dyslipidaemia have been found to be risk factors for the development and progression of diabetic retinopathy (Ciulla *et al.*, 2003). HIV infection has been shown to increase the chances of developing diabetes (Mash, De Vries and Abdul, 2007), although the relationship with diabetic retinopathy has not been investigated. The Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR) indicated that the prevalence of diabetic retinopathy is significantly greater in Type II diabetics on insulin therapy compared to Type II diabetics not on insulin therapy (Mollentze, 2003). Aspelund *et al.* (2011) found that type, duration of diabetes, HbA1c, systolic blood pressure, sex and the degree of diabetic retinal change were associated with progression of diabetic retinopathy. Table 1 below summarises the global evidence on the risk factors for diabetic retinopathy

Table 1: Diabetic retinopathy risk factors identified by various studies

Risk Factors	ET-DRS	Davis *et al*	Van Leiden *et al.*	Aspelund *et al.*	Mollentze	Mehlsen *et al.*	Ciulla *et al.*
Age	x						
Gender				x		x	
Decreased Visual Acuity		x					
Insulin dependant	x			x	x		
Duration of diabetes	x			x	x	x	
Abdominal obesity			x				
Hyperglycaemia			x	x			x
HBA1c	x	x		x		x	
Hypertension			x	x		x	x
Dyslipidaemia							x

The risk factors which have been associated with the onset and duration of diabetic retinopathy in previous studies have not been quantified and the pathophysiology and pathways by which these risk factors impact retinal changes in diabetics are still being debated (Ciulla *et al.*, 2003).

Aspelund *et al.* (2011) assessed risk factors for progression of diabetic retinopathy in order to safely customise the DRS interval, and found that a mathematical algorithm utilizing the data of these known risk factors: HbA1c, waist-hip ratio and hypertension, allows one to safely customize individual DRS intervals. The use of customised DRS intervals reduced the annual number of diabetics to be screened by 40% (Looker *et al.,* 2013). Similarly, Mehlsen, Erlandsen, Poulsen and Bek (2011) in their research to individually customize the DRS interval, investigated the following risk factors: diabetes type, onset and duration of diabetes, gender, HbA1c, blood pressure and severity of diabetic retinopathy. Of these, the degree of diabetic retinopathy, HbA1c and the patient's age at diagnosis were associated with the progression of diabetic retinopathy. On the basis of these findings, more effective and efficient approaches to the delivery of the DRS were developed. These studies highlight the value of investigating risk factors associated with treatment requiring diabetic retinopathy not only as a pre-screening tool but also as a predictor of diabetic retinopathy progression.

BARRIERS TO DIABETIC EYE CARE

Current guidelines dictate that all diabetics require regular comprehensive ocular examinations, which may be conducted by a well-trained cadre of health personnel including: community health workers, optical dispensers, retinal camera technicians, primary health care nurses, optometrists, medical officers and ophthalmologist (NDOH, 2002). This is achievable if the health system structures are in place which encompass the necessary equipment, qualified health personnel, appropriate referral pathways and patient education. Cook (2013) divides DRS programmes into either structured or opportunistic, where structured involves a clearly defined systematic approach detailing the various referral pathways and opportunistic alluding to the availability of fundal imagery but without the emphasizes on collaboration between the various stakeholders. The current DRS programme in the MDHS can be regarded as a combination of both, where DRS is available at primary health care level but with poor attendance and inadequate identification of high risk profile patients.

Apart from the MDHS programme, the only other DRS programme described on the African continent from which to draw insights is the Kilimanjaro Diabetic Programme (KDP) in northern Tanzania. This project mimics the modus operandi of the MDHS DRS programme, whereby retinal screening teams go to public health facilities to capture the fundal images with a mobile camera. The KDP reported a low attendance rate in those diabetics who were referred for ophthalmic treatment, which highlights the need for future studies to clearly identify referral pathways (Cleland *et al.*, 2016).

In Finland, the Diabetic Retinopathy Barometer project found that even in this developed country setting, there is poor integration of eye care services with diabetic case management, with illogical investment in tertiary health care focussing on treatment rather than prevention and early detection at lower levels of the system.

KNOWLEDGE GAP

Risk factors associated with treatment-requiring diabetic retinopathy in the specific context of the public health sector in South Africa are not well established. While Aspelund *et al.* (2011) showed that in Denmark it was possible to extend the DRS interval in certain cases with the use of the extrapolated individual risk factors, at present there are no such pre-screening tools for the South African public sector context which make use of available clinical information. An accurate pre-screening algorithm will enable the selection of cases that would benefit the most from laser photocoagulation treatment.

CHAPTER THREE: METHODOLOGY

STUDY DESIGN

A case-control study was conducted to establish the difference in levels of exposure to possible risk factors for treatment requiring diabetic retinopathy, where cases were those judged as requiring laser treatment and controls as those not requiring laser treatment, based on fundal photography.

STUDY POPULATION

The study population was all diagnosed Type II diabetics receiving their treatment from a public primary health care facility situated within the Klipfontein and Mitchells Plain Sub-Districts of the Metro District Health Services (MDHS), and meeting the following inclusion and exclusion criteria.

Inclusion criteria:

Diagnosed Type II diabetics using anti-diabetic medication; resident within the Klipfontein and Mitchells Plain Sub-Districts of the Cape Town Metropolitan District; had undergone fundal photography screening in the study period.

Exclusion criteria:

Type I diabetics; Type II diabetics in which the fundal photographs were un-gradable; Type II diabetics receiving their medication at a tertiary health care institution; Type II diabetics who have already had laser photocoagulation performed on one of their eyes.

DEFINITION OF CASES AND CONTROLS

Cases constituted Type II diabetics who attended the Diabetic Retinopathy Screening (DRS) programme and presented with retinopathy requiring treatment based on the Scottish Grading Scale of their fundal images; provided that they met the inclusion criteria. Controls were the consecutive attendees of the DRS programme (i.e. after the cases) in the same facility who presented with normal retinal appearance or mild changes not requiring treatment based on the Scottish Grading Scale.

SAMPLE SIZE

Using the statistical calculator on Epi Info 7, the following information was entered: case to control ratio of 1:3; risk factor prevalence in the controls of 50%; confidence interval of 95%; statistical power of 80% and an estimated odds ratio of 2. This amounted to a study sample size of at least 398 participants constituting 100 cases and 298 controls.

SELECTION AND MATCHING OF CASES AND CONTROLS

Cases and controls were selected from the diabetic patients participating in the DRS programme from February to November 2015. In this period, 3 378 diabetic patients in nine clinics of the Klipfontein and Mitchells Plain Sub-Districts were screened. Of these, 381 (11%) were identified on fundal photography as having an ocular disorder requiring further treatment, including, but not limited to diabetic retinopathy. Of these, 185 satisfied the inclusion and exclusion criteria and case definition. The cases were individually matched with controls by area of residence in a ratio of 1:3. This allowed for the control of both health service accessibility and socio-economic status of the participant. These variables have been associated with the prevalence of visual loss found in different communities in Cape Town (Cockburn *et al.,* 2012).

DATA COLLECTION AND COLLATION

Fundal Photography

The retina of diabetic patients was photographed with the use of a mobile fundal camera (Canon CRII non-mydriatic fundus camera) operated by a retinal camera technician with an ophthalmic dispensing diploma. An assistant recorded patient information on a standardised sheet. The fundal images concentrated on the central and para-central retina, thus allowing for the view of the macula and optic nerve head on a single image; for most images the far circumferential retinal periphery was not captured. The majority of patients had two images taken- one image per eye. The patients who presented with media opacities e.g. cataracts, corneal defects, were dilated with the use of 10mg Tropicamide (Mydriacyl) to allow for a better image quality.

The researcher, an employee of the eye care service provider for the particular sub-district throughout the study period, was tasked with the grading of all the fundal images. The grader was blind to the information pertained in the patients' folders at the time of the grading.

Patient record cards (collated in an alphabetic order) and a flash disk were handed to the retinal grader on a daily basis, who assessed each image, recorded findings and made recommendations.

The Scottish Grading Scale was used to grade the diabetic retinal changes. This is appropriate for grading fundal photographs of the posterior pole and defines the degree of diabetic retinopathy in a hierarchical manner including the appearance of the macula (Cook, 2013). The standard grading procedure included categorising the images into four categories:

- No Diabetic Retinopathy detected – annual examination recommended
- Mild to Moderate Diabetic Retinopathy with no maculopathy – 3/6 months' follow-up fundal imagery recommended
- Severe Non-Proliferative Diabetic Retinopathy – referral to ophthalmology
- Proliferative Diabetic Retinopathy – referral to ophthalmology

The first two categories constituted controls and the second two categories cases.

Record Review

The data obtained from each batch of images graded per CHC was collated daily in a spreadsheet, and a copy of these clinical records stored at the service provider's base located at Woodstock Hospital. In December 2015, the researcher assembled all the cases meeting the case definition over the study period and selected three to four controls from the patients seen immediately after the case on the same day. Subsequently, all potential study participants were contacted telephonically to inform them that they had been selected and requesting consent to review their clinical folder in the facility. The clinical records were reviewed between January and March 2016 by the researcher at each participating facility. A data extraction form was designed (Appendix C) and attached to the back of the eye health record card. The data of the variables being investigated were entered and organised in a spread sheet along with the other relevant clinical information.

Table 2 below lists the data collected/variables studied and their definition

Table 2: Data/variables and definitions

Variable	Measurement
Age	The date of birth was used as reference, and the patient's age in the year 2015 was recorded.
Sex	The patient's gender depicted on their clinical sticker was recorded.
BMI	This variable is a product of two separate variables: weight (kg)/ height $(m)^2$.The height of the patient in meters rounded to the second decimal was obtained in the clinical folder and recorded by a clinical nurse using a wall length tape. The most recent weight in kilograms rounded to the first decimal was obtained from the most recent scale measurements conducted by the clinical staff and recorded in the folder. Subsequently, weight (kg)height with each participant's data were calculated to obtain the BMI figure rounded to one decimal point.
Co- morbidities	The co-morbidities were recorded based upon the diagnosis and medicine recorded on the participants' recent chronic dispensing chart, as signed off by the attending medical officer. This categorical data was recorded in excel spreadsheet.
Insulin dependency	This was recorded as the absence or presence of insulin-therapy on the patient's latest chronic dispensing chart.
Duration of diabetes	The duration of diabetes was taken as the time from the start of anti- diabetic treatment. The duration of diabetes was ascertained by direct questioning of the patient on the day of the fundal photography by the Retinal Camera Imagery (RCI) team, and then verified by reviewing the folder of the participants at their respective clinics during the data collection phase of the study. Due to the inconsistent nature of record keeping compounded by the problem of recall by the patient on the day of the fundal imagery, duration was recoded into 5 year intervals.
Smoking Status	The smoking of tobacco products as recorded in the clinical folder was recorded as a binary (yes/no) variable.
Glycated haemoglobin levels	This was recorded as percentages up to one decimal point. This reading was taken from the last clinical laboratory results filed within the patients' folder provided that it was done within the last two years.
Blood-plasma glucose levels	This data was taken as the average of the three most recent measurements for each participant with the time-span of these findings ranging at most from six months to at least a week. This was recorded up to the first decimal.

RELIABILITY AND VALIDITY

The reliability and validity of the study was enhanced through:

- Recording data using standardised measurement equipment i.e. measuring tape/weight scale was similar in make or to assign one piece of equipment per data item being measured.
- Adopting the gold standard for retinal imagery.
- The retinal camera technician was blinded to the participants of the study as images were collected prior to selection of cases.
- A single retinal grader viewed the fundal images.
- Verification of the data through reviewing the study participants' folders to lessen recall bias on e.g. treatment received and comorbidities.

GENERALISABILITY

The Klipfontein and Mitchells Plain Sub-Districts are two of the eight Sub-Districts which form part of the Cape Town MDHS, and the findings are generalizable to these Sub-Districts. However, the study participants are likely to exhibit similar characteristics to diabetic patients attending the Primary Health Care (PHC) facilities in the other Sub-Districts and are likely to be applicable to Type II diabetics receiving care at the different PHC facilities within the MDHS.

DATA ANALYSIS

Data were entered and organized in an excel spreadsheet and checked for errors and missing data. Analysis was done with the help of a statistician using the NCSS 9 Statistical Software, which incorporates regression modelling.

The description of the categorical data i.e. sex, duration, type, co-morbidities and smoking was done through frequency distribution and the differences between cases and controls assessed using the Pearson's Chi Square test.

The normality of distribution of the continuous data was assessed with the use of the D'Agostino Skewness test. The data indicating a rejection of normality was then transformed into logarithmic values. The description of the continuous data i.e. age, BMI, blood glucose level and HbA1c was done through the calculation of the mean, range and 95% confidence

intervals. Linear regression was then performed to assess the differences between cases and controls.

Those variables/risk factors that were significantly associated at the 5% level with the presence of treatment requiring retinopathy (cases) were entered into a multiple regression model and multivariate analysis conducted.

SENSITIVITY AND SPECIFICITY

Variables which remained significantly different between cases and controls following multivariate analysis were combined in various permutations as algorithms for identifying those who should be prioritised for the DRS programme. The algorithm was then tested for sensitivity (the ability to identify those with disease), specificity (the ability to exclude those without disease), and positive and negative predictive values (the proportions with and without the disease).

ETHICS

The Senate Research Committee of the University of the Western Cape approved the methodology and ethics of this research project in June of 2015 (Appendix B). Subsequently, I applied for ethical clearance from the Western Cape Provincial Department of Health to allow me to access the participants' folder at the relevant facilities, and also obtained the consent of facility managers.

The delay in approval from the relevant clinics resulted in my altering the data collection from achieving the collection of data on the same day as the fundal imagery. Eventually, permission was obtained to access the facilities in December 2015, which meant that I had to obtain my consent telephonically and retrospectively obtain the data.

The selected participants in the study were contacted telephonically in December 2015 and informed about the study and what their involvement would entail (Appendix A). Once the patient gave verbal consent this was recorded on the eye health record card which contained the participant's contact details and to which the data collection form was attached. The participants were reassured that the information obtained from their folder would be kept private and confidential. In the analysis all identifiers were removed and data reported in aggregated form.

The routine standard of care (referral for treatment) was strictly adhered to in patients with retinal abnormalities requiring treatment.

The results of this study once finalised will be fed back to the clinical programme managers who will take responsibility to disseminate the information to all parties involved.

LIMITATIONS

The retrospective nature of the data collection which entailed folder review did result in a greater level of inaccurate or missing data. This was recorded in Excel spreadsheet as missing. Information relating to the duration of diabetes was difficult to verify and could only be recorded as less or more than a specific year. Active clinical folders have records pertaining to the last twenty years (presumably then placed in storage due to the bulkiness) which impedes the accuracy of information on the onset of diabetes of those receiving diabetic treatment for more than twenty years.

The blood glucose level values were susceptible to fluctuation due to absence of conformity with regard to time of day and history of food consumption prior to the test. A more accurate measurement of the patients' glycaemic level is the HbA1c level. However, due to lack of consistent HbA1c testing of diabetic patients amongst and within clinics a high amount of data was missing. This is possibly due to the complex process involved. The majority of diabetics had had HbA1c analysis before, however a substantial number has not had one in the last year when the data was collected, therefore the variable for the participant was recorded as missing.

Although weight was routinely measured at the clinic, height was somewhat neglected, most likely due to emphasis being placed on monitoring the fluctuation of an individuals' weight in contrast to the consistency of an individuals' height. Participants who are wheelchair-bound rarely had their height and weight measured. This made it difficult to assess BMI.

Visual Acuity (VA) were collected as part of the routine DRS programme, but not analysed as the study took into consideration routinely measurable systemic markers performed by primary health care workers. In certain instances, participants had duplicate folders at their clinic which led to gaps in a patients' clinical history impacting on data collection.

CHAPTER FOUR: RESULTS

The results section first analyses the distribution of cases and controls by facility, age and sex. It then compares their clinical and risk factor profiles and distribution of co-morbidities. Significant differences between cases and controls are then analysed in a multivariate model. Finally, clinical variables showing significant differences between cases and controls are tested in different combinations to assess their performance as a pre-screening tool for prioritising patients for fundal photography.

DISTRIBUTION OF STUDY SAMPLE

During the study period, 3378 diabetics underwent retinal camera imagery, of whom 381 (11.3%) presented with ocular pathology e.g. cataracts and diabetic retinopathy, which required further investigation and intervention by an ophthalmologist. Of these, 185 satisfied the inclusion criteria as cases i.e. diabetic retinopathy requiring treatment. A total of 113 consented to participate in the study, giving a response rate of 61.1%. Of the 439 controls who were contacted, 340 (77.5%) consented to participate.

Table 3 gives the distribution of the study sample by facility. The number of diabetics attending the Diabetic Retinopathy Screening (DRS) in the study period differed by clinic, depending not only upon the total number of diabetics receiving their health care at the particular clinic, but also on the availability of space and resources to host the fundal imagery. Mitchells Plain CHC contributed one-fifth of the diabetics screened, while Nyanga CHC, where the DRS programme only started in June of 2015, had the lowest number of screenings conducted.

During case selection three to four controls (depending on availability) were selected from the same screening batch matched for area of residence. As Table 3 indicates, the distribution of the study sample more or less reflects the distribution of the screening programme in the clinics. The lowest proportion of participants garnered from the screened population was at Cross Roads CHC, which was in part due to poor rate of retrieval of the folders upon review.

Table 3: Distribution of diabetics screened (n = 3 378), cases (n=113) and controls (n=340) by clinic

Name of clinic	Diabetics screened (% total)	Cases (% total)	Controls (% total)	Total sample (% total)
Cross Roads (CRC)	228 (6.8)	3 (2.7)	4 (1.2)	7 (1.6)
Dr Abdurahman (DAC)	506 (15.0)	14 (12.4)	62 (18.2)	76 (16.8)
Gugulethu (GDH)	305 (9.0)	17 (15.0)	41 (12.0)	58 (12.8)
Hanover Park (HPH)	437 (13.0)	9 (8.0)	25 (7.4)	34 (7.5)
Heideveld (HVP)	507 (15.0)	9 (8.0)	43 (12.7)	52 (6.6)
Inzame Zabantu (IZC)	326 (9.7)	9 (8.0)	21 (6.2)	30 (6.6)
Mitchells Plain (MHC)	690 (20.4)	28 (24.8)	90 (26.5)	118 (26.1)
Nyanga (NGC)	69 (2.0)	7 (6.2)	12 (3.5)	19 (4.2)
Tafelsig (TAF)	310 (9.2)	17 (15.0)	42 (12.4)	59 (13.0)
Total	3 378 (100)	113 (100)	340 (100)	453 (100)

AGE-SEX PROFILE OF CASES AND CONTROLS

The majority of study participants were 50 years or older (Table 4). There were few participants under the age of 30 years, as Type I diabetics who present at a younger age were excluded from the study population. There was a statistically significant difference in mean age between the cases (58.2 years) and controls (55.6 years) (p-value = 0.043).

There were three times more female participants than male participants in the overall sample, but there were no differences in the sex distribution between cases and controls.

Table 4: Age-sex profile of total sample (n = 453), cases (n = 113) and controls (n = 340)

Variable			Cases (% total)	Controls (% total)	P -Value
Age	Distribution	20-29	0 (0.0)	3 (0.9%)	
		30-39	1 (0.9)	14 (4.1)	
		40-49	17 (15.1)	44 (12.9)	
		50-59	36 (31.9)	133 (39.1)	
		60-69	48 (42.5)	104 (30.6)	
		70-80	11 (9.7)	40 (11.8)	
		>80	0 (0.0)	2 (0.6)	
		Total	113 (100)	340 (100)	
	Mean Age (Years)		58.2	55.6	0.043
	95% CI*(%)		56.5 – 59.9	54.6 – 56.6	
	Range		38 – 80	23 – 82	
Sex	Female		88 (77.9)	261 (76.8)	0.808
	95% CI (%)		69.2 - 86.6	71.7 - 81.9	
	Male		25 (22.1)	79 (23.2)	
	95% CI (%)		5.8 - 38.4	13.9 - 32.5	

*Confidence Interval

The difference in age distribution between cases and controls is further illustrated in Figure 1, indicating the skewed distribution towards older age groups of the cases.

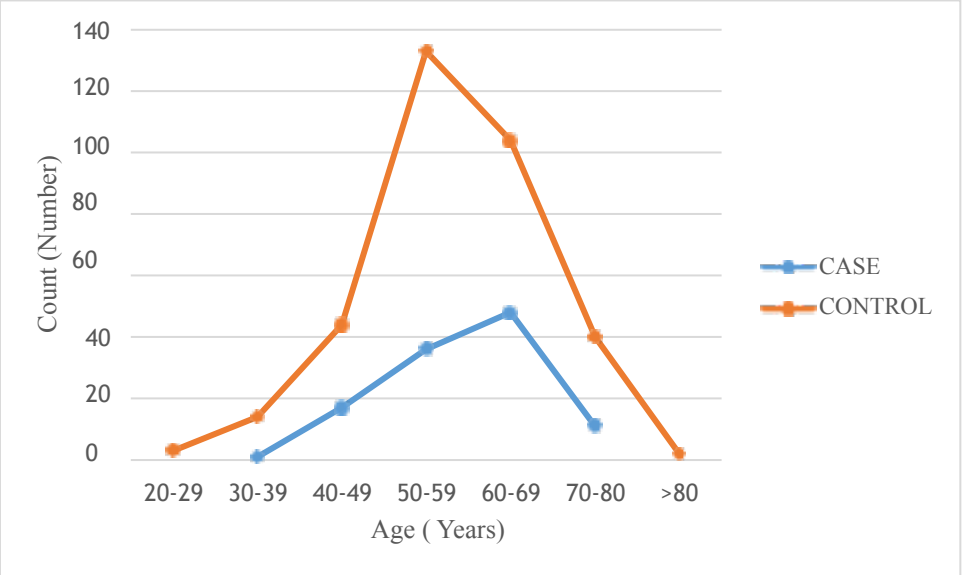

Figure 1: Age distribution of cases (n=113) and controls (n=340)

There were also statistically significant differences in mean ages between clinics (p = 0.001). Two clinics - Cross Roads (CRC) and Inzame Zabantu (IZC) - had younger patient populations (for both cases and controls). In a further two clinics - Mitchells Plain (MHC) and Hanover Park (HPH) - the mean age of the controls was slightly higher than the cases (Figure 2).

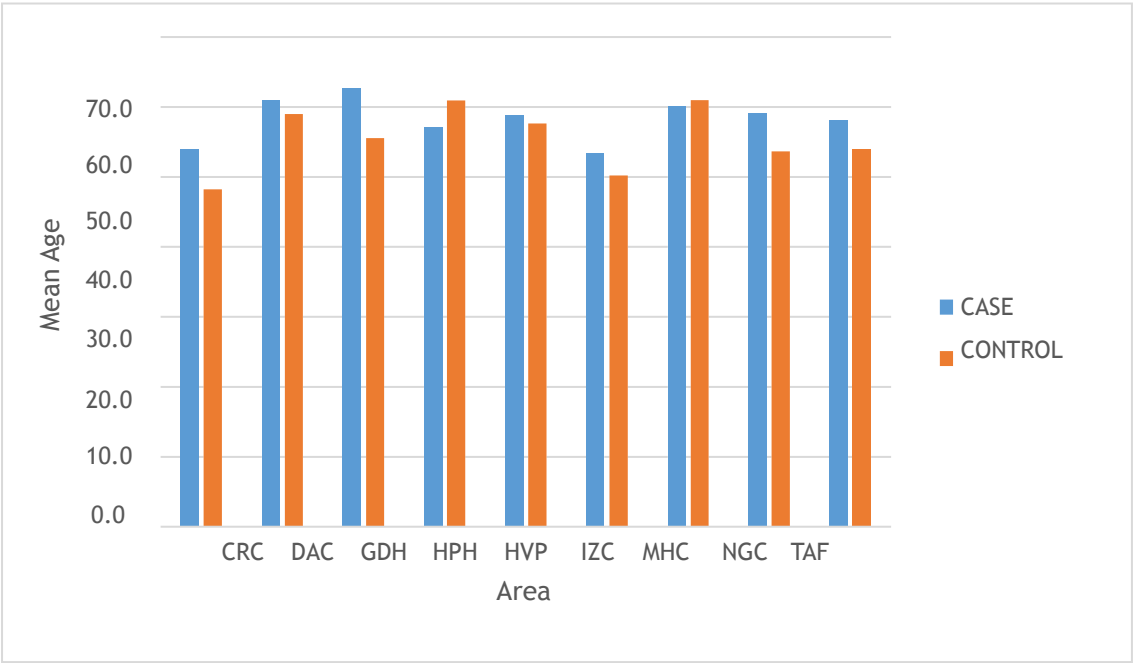

Figure 2: Mean age of cases and controls per clinic

CLINICAL PROFILE OF CASES AND CONTROLS

The clinical profile of cases and controls, with respect to the duration of diabetes, the dependency on insulin, and blood glucose and HbA1c levels is shown in Table 5.

Duration of diabetes (Table 5) was categorised into less than five years, between five and ten years and more than ten years. There was a significant difference in the proportion of cases and controls who had been on anti-diabetic treatment for ten years or more. Cases were twice as likely to have been on treatment for ten years or more (Pearson's Chi-Square, $p < 0.001$).

The usage of insulin was recorded as a binary variable (Yes/No) without taking into consideration the duration that the patient may have been on insulin therapy, nor the type of insulin and dosage currently being used by the patient. There was also a marked and significant difference between cases and controls in the usage of insulin (Pearson's Chi- Square, $p < 0.001$).

Table 5: Clinical profile of sample (n = 453) cases (n = 113) and controls (n=340)

Variable	Category		Cases (% total)	Controls (% total)	P Value
Duration of Diabetes (years)	Missing		10 (9.7)	34 (10.0)	
		95% CI (%)	0.0 - 27.2	0.0 - 20.1	
	0 – 4.99		13 (12.6)	107 (35.0)	
		95% CI (%)	0.0 - 29.8	26.4 - 43.6	
	5 – 9.99		24 (23.3)	110 (36.0)	
		95% CI (%)	7.1 - 39.5	27.5 - 44.5	
	10+		66 (64.1)	89 (29.1)	
		95% CI (%)	53.0 - 75.2	20.1 - 38.1	< 0.001
	Total		113 (100)	340 (100)	
Insulin Dependency	Yes		79 (69.9)	111 (32.7)	
		95% CI (%)	59.8 - 80	24.0 - 41.4	
	No		34 (30.1)	229 (67.4)	
		95% CI (%)	14.7 - 45.5	61.3 - 73.5	
	Total		113 (100%)	340 (100%)	< 0.001
Blood Glucose Level (mmol/L)	Mean		12.5	10.6	
	95% CI		11.7 – 13.3	10.2 – 11.0	
	Range		5 – 24.5	4 – 20.5	
	Logarithmic Mean		2.5	2.3	0.023

	95% CI	2.4 – 2.6	2.3 – 2.4	
	Range	1.6 – 3.2	1.4 – 3.0	
HbA1C (Percentage)	Mean	10.6	9.5	
	95% CI	10.1 - 11.1	9.2 – 9.8	
	Range	5.4 – 17.8	5 – 17.3	
	Logarithmic Mean	2.3	2.2	0.014
	95% CI	2.2 – 2.3	2.1 – 2.2	
	Range	1.7 – 2.9	1.6 – 2.9	

The distribution of mean blood glucose levels of the total sample is indicated in Figure 3. Due to significant outliers and skewness in the distribution of data, neither the cases nor the controls passed the normality test (D'Agostino Skewness) for distribution of blood glucose levels. Logarithmic values were thus computed producing a better distribution (Figure 4) and a more valid use of tests of statistical significance. Linear regression of the mean logarithmic value of blood glucose for cases and controls indicated a statistically significant difference between cases and controls (p=0.023).

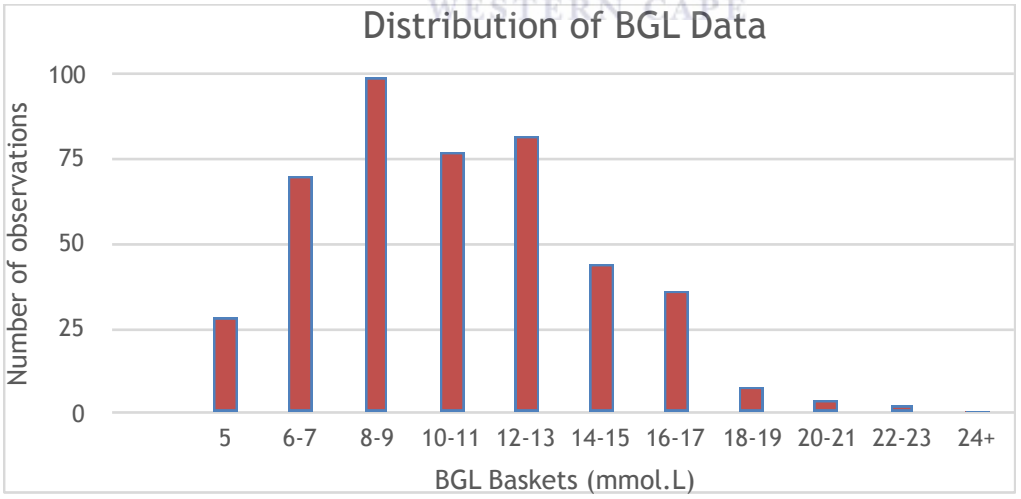

Figure 3: Distribution of the sample's mean blood glucose levels (cases and controls combined)

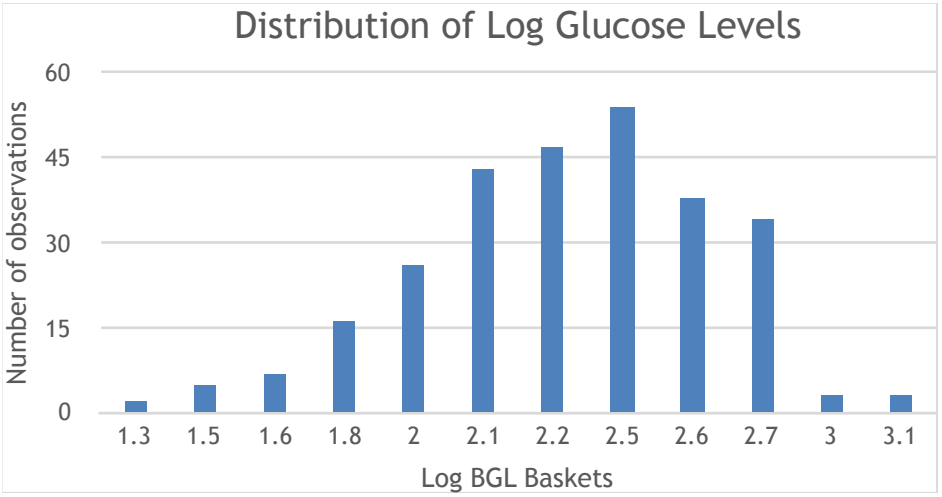

Figure 4: Distribution of the sample's blood glucose levels after logarithmic transformation

Data were available on HbA1c levels for 88 out of the 113 cases (77.9%) and 285 out of the 340 controls (83.8%). The distribution of the HbA1c data similarly did not pass the D'Agostino Skewness test, and the HbA1c data was also transformed into logarithmic values before tests of association applied. Statistically significant differences in the mean logarithmic values of the HbA1c data were also found amongst the cases and controls (p-value = 0.014).

RISK FACTORS IN CASES AND CONTROLS

There was no statistically significant difference (P=0.698) in current smoking status between cases (31.4%) and controls (29.4%) (Table 6).

Data on BMI was available for 96.5% and 95.3% of cases and control respectively. The mean BMIs for both cases (30.9) and controls (32.7) were in the obese range, and differences were not statistically different (p=0.163).

Table 6 : Risk factors of sample (n = 453) cases (n = 113) and controls (n = 340)

Variable	Category	Cases (% total)	Controls (% total)	P-Value
Smoking Status	Missing	8 (7.6)	24 (7.1)	
	95 % CI (%)	0.0 - 25.3	0.0 - 17.3	
	Not Smoking	72 (68.6)	223 (70.6)	
	95 % CI (%)	58.3 - 78.9	64.8 - 76.4	
	Smoking	33 (31.4)	93 (29.4)	
	95 % CI (%)	16.1 - 46.7	20.5 - 38.3	0.698
Total		113 (100)	340 (100)	
Body Mass Index	Mean	30.9	32.7	
	95% CI	29.5 – 32.3	31.9 – 33.5	
	Range	18.2 – 54.1	16.7 – 57.0	
	Logarithmic Mean	3.4	3.5	0.163
	95% CI	3.4 – 3.4	3.5 – 3.5	
	Range	2.9-4.0	2.8-4.0	

CO-MORBIDITIES IN CASES AND CONTROLS

Co-morbidities were highly prevalent in the study population, with only 1 case and 19 controls not receiving treatment for a condition other than diabetes (Table 7). There were 224 instances of co-morbidity (mean 1.98 per person) for cases and 669 (mean 1.97 per person) for controls. A very high percentage of both cases (96.5%) and controls (86.8%) received anti-hypertensive treatment. Furthermore, treatment for cholesterol and osteoarthritis was also common for both cases and controls. Linear regression indicated a statistical significant difference in hypertension treatment between cases and controls (p= 0.004).

Table 7: Treatment for co-morbidities in cases (n=113) and controls (n=340)

Co-morbidity	Total	Case	Control	P-Value
Hypertension	404 (89.2%)	109 (96.5%)	295 (86.8%)	P=0.004
95% CI	86.2% - 92.2%	93.0% - 100%	82.9% - 90.7%	
Osteoarthritis	184 (40.6%)	36 (31.9%)	148 (43.5%)	P=0.029
95% CI	33.5% - 47.7%	16.7% - 47.1%	35.5% - 51.5%	
Cholesterol	102 (22.5%)	32 (28.3%)	70 (20.6%)	P=0.08
95% CI	14.4% - 30.6%	12.7% - 43.9%	11.1% - 30.1%	
Ischemic Heart Disease	49 (10.8%)	17 (15.0%)	32 (9.4%)	
Chronic Obstructive Pulmonary Disease	33 (7.3%)	9 (8.0%)	24 (7.1%)	
Gastro- oesophageal reflux disease	33 (7.3%)	4 (3.5%)	29 (8.5%)	
None	20 (4.4%)	1 (0.9%)	19 (5.6%)	
Asthma	14 (3.1%)	2 (1.8%)	12 (3.5%)	
Congestive Cardiac Failure	13 (2.9%)	5 (4.4%)	8 (2.4%)	
Hypothyroidism	7 (1.5%)	1 (0.9%)	6 (1.8%)	
Benign Prostate Hypertrophy	6 (1.3%)	3 (2.7%)	3 (0.9%)	
Epilepsy	6 (1.3%)	1 (0.9%)	5 (1.5%)	
Gout	6 (1.3%)	0 (0%)	6 (1.8%)	
Depression	6 (1.3%)	3 (2.7%)	3 (0.9%)	
Rheumatoid Arthritis	5 (1.1%)	1 (0.9%)	4 (1.2%)	
HIV/Aids	5 (1.1%)	0 (0%)	5 (1.5%)	

MULTIVARIATE ANALYSIS AND SCREENING MODELS

Significant differences between cases and controls on bivariate analysis were entered into a multivariate logistic regression model (Table 8). These included factors which remained significantly associated with diabetic retinopathy in the multiple regression model: duration of diabetes of more than ten years, insulin dependency and the log value of blood glucose level. Blood glucose levels were chosen rather than HbA1c for inclusion in the model, due to the large amount of missing HbA1C data.

Linear regression indicated statistically significant differences in treatment for hypertension (p=0.004) and osteoarthritis (p=0.029) between cases and controls. However, when combined with other factors on multivariate analysis these factors were no longer associated with treatment-requiring diabetic retinopathy and were excluded from the development of the screening algorithm.

Table 8: Factors associated with treatment requiring retinopathy: multi-variate analysis (controls =0, cases=1)

Variable	Regression Coefficient	Standard Error	Adjusted Odds Ratio	Lower 95% Limit	Upper 95% Limit	P - Value
Age	0.01	3.43	1.01	0.97	1.04	0.68
Duration of diabetes >=10 years	1.23	0.26	3.44	2.06	5.74	<0.001
Insulin dependency	1.08	0.27	2.96	1.75	5.00	<0.001
Log Blood Glucose	1.32	0.40	3.73	1.69	8.22	0.001

The three risk factors for treatment-requiring diabetic retinopathy - duration of diabetes treatment, insulin dependency and blood glucose level - were combined in various permutations and assessed as a screening algorithm to identify at risk patients who could potentially be fast- tracked for fundal imagery.

Firstly, the variables have to be combined into different categories to identify the best grouping to detect a case i.e. presenting with treatment-requiring diabetic retinopathy. A challenge is to redefine the cut-off for the blood glucose level to aid with the grouping and to fit with the two other binary variables.

Three algorithms are presented in Table 9, with their performance in terms of sensitivity (ability to pick up cases needing to be prioritised), specificity (the ability to exclude those without disease), and positive and negative predictive values.

The first algorithm makes use of insulin dependency and duration of diabetes equal to or more than ten years, and excludes blood glucose level as a parameter.

The second algorithm combines insulin dependency, duration of diabetes of more than ten years and blood glucose level greater than 8 mmol.L. The therapeutic goal of anti-diabetic treatment for blood glucose level is aimed at a fasting blood glucose level of 8 mmol.L.

The third algorithm combines the duration of diabetes of more than five years, insulin dependency and blood-glucose level average of equal or more than 8 mmol.L.

Table 9: The measures of validity for the different algorithms

Algorithm Versions	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Version 1	50.5 (95% CI: 40.8 - 60.2)	85.0 (95% CI: 81.0 - 89.0)	53.1	83.6
Version 2	48.5 (95% CI: 38.8 - 58.2)	88.9 (95% CI: 85.4 - 92.4)	59.5	83.7
Version 3	61.2 (95% CI: 51.9 – 70.5)	76.8 (95% CI: 72.1 - 81.5)	47.0	85.5

The highest sensitivity achieved with the different permutations were with the third algorithmic version. Figure 5 below clearly indicate that the specific combination of variables used for the third algorithm show that 65% of all cases fall into that category.

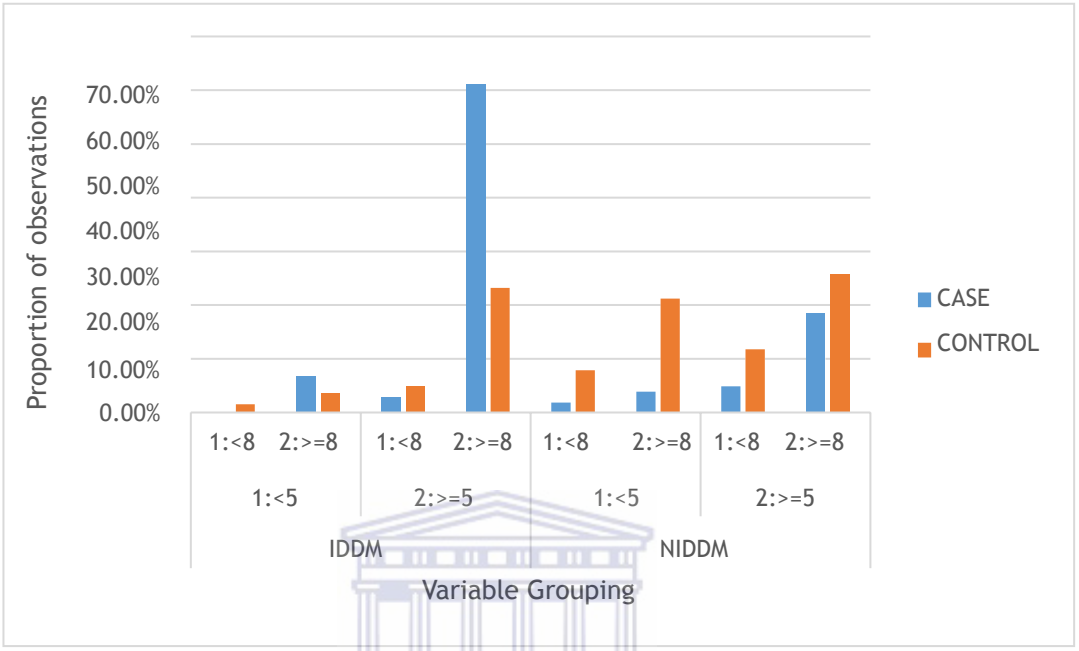

Figure 5: Statistical significant variable groupings with proportion of cases and controls per grouping.

This indicates that incorporating the third algorithm as a pre-screening tool we shall correctly identify two-thirds of the cases. More than 20% of the controls also fall into that category, which means that there shall be false positives identified as well.

CHAPTER FIVE: DISCUSSION

There have been numerous large scale studies quantifying risk factors for diabetes and subsequent onset of complications (Mash and Levitt, 2003). However, there is little research on the relationship between biomarkers and diabetes onset and subsequent diabetic complications within the South African context. Moreover, studies have tended to group the wide variety of diabetes complications together and examined associations for all simultaneously (Mash, 2010).

A hierarchical approach to research on diabetic complications seems to exist with macro-vascular complications such as myocardial infarction receiving more attention (in research) than micro-vascular complications such as diabetic retinopathy. This could be due to the focus on life-saving interventions, combined with the historical difficulty of measuring diabetic ocular complications and the presumption of inevitable ocular complications regardless of risk factor control (Mollentze, 2003).

This study sought to establish risk factors associated specifically with treatment-requiring diabetic retinopathy based on fundal imagery. The study included 453 participants, of whom 113 (24.9%) were cases and 340 (75.1%) were controls. The majority of the study participants were over the age of 50 years. This age profile is similar to that found in the South African National Health and Nutrition Examination Survey (SANHANES-1) (NDOH, 2012), which found that the rate of diabetes increased almost five fold from 45 to 65 years of age for both male and females. The study participants included three times more females than males. The SANHANES-1 (NDOH, 2012) also found that females constitute the majority of the Western Cape diabetic population, although this ratio was less pronounced than that of the study participation (1.3:1). This suggests that there was an over-sampling of females which might indicate the poor attendance of the DRS programme by males. The mean body mass index in both cases and controls was greater than 30, indicating high level of obesity amongst the study participants. However, obesity is also high in the general population. Western Cape's female population has shown to have a prevalence of obesity (BMI > 30) of 37.9% (NDOH, 2012).

Just under a third of cases and controls were recorded as being smokers, similar to background levels for the Western Cape (NDOH, 2012).

The risk factors investigated were those identified through literature review indicated to be associated with the onset of diabetes and the associated complications, and are routinely (in most instances) measured at clinic level and readily available to the health work force.

Three factors were significantly associated with treatment-requiring diabetic retinopathy on multivariate analysis: Insulin dependency (OR of 2.96, 95% CI: 1.75 – 5.00); duration of diabetes of more than 10 years (OR of 3.44, 95% CI: 2.06 – 5.74) and sustained hyperglycaemia over the past six months (OR of 3.73, 95% CI:1.69 – 8.22).

Cases were significantly older than controls on linear regression. However, on multivariate analysis this association disappeared. The Early Treatment of Diabetic Retinopathy Study (ETDRS) found age to be a significant factor in the progression of diabetic retinopathy. The age of onset of diabetes was shown to be more important than the actual age of the patient, which is more an indication of the duration of diabetes (Mehlsen *et al.,* 2011).

Gender of the study participants had no influence on the presentation of treatment-requiring diabetic retinopathy. This is in contrast to Mehlsen *et al.* (2011) who found a higher proportion of treatment-requiring diabetic retinopathy amongst men than women, and the United Kingdom Prospective Diabetic Study (UKPDS) where the incidence of diabetic retinopathy was higher in men than women. Given the relatively low ratio of men to women in the study population of the current study, one possible explanation is that those men most at risk are not attending health services.

This research found that type II diabetics on anti-diabetic treatment for more than ten years have a higher likelihood to present with treatment-requiring diabetic retinopathy than those on treatment for less than ten years. This has been found in other studies (Ciulla *et al.,* 2003). The exact mechanism of how diabetes effects changes to the retina is not clear, however it is commonly taken that these changes do occur over a period of time and that the changes follow a natural progression. Mehlsen *et al.* (2011) found in their research to optimize the DRS interval that type II diabetics reached a treatment end-point in a shorter time frame than type I diabetics.This might be explained by the delayed diagnosis of type II diabetes.

Insulin dependency was statistically associated with the presentation of treatment-requiring diabetic retinopathy. Aspelund *et al.* (2011) as well as the ETDRS also found the usage of insulin in type II diabetics as a risk factor for diabetic-related complications.

Whether the association is due to the usage of insulin as treatment or an indication of poor blood-glucose control is not well established.

The American Diabetes Association (1998) has pointed out that the association of hyperglycaemia and diabetic-related complications was well established in the early part of the twentieth century. However, only recently has that association been investigated through observational/experimental studies on both animal and humans alike, and the strength of association quantified. The more accurate indication of hyperglycaemia is given by the individual's HbA1c level. However, due to the significant number of individuals' HbA1c level missing on data collection, this could not be considered in the multivariate analysis.
Mehlsen *et al.* (2011) found that elevated HbA1c is significantly associated with diabetic retinopathy requiring treatment. The United Kingdom Prospective Diabetes Study (UKPDS) the largest study concerned with the relationship between glycaemic control and diabetic-related complications in Type II diabetics found that the extent of the glycaemic control is also important, i.e. the level of reduction in HbA1c reading: for every percentage of HbA1c lowered there is 35% reduction in risk of microvascular complications and a 25% reduction in diabetes-related death (American Diabetes Association, 1998).

The UKPDS did not propose a glycaemic threshold, suggesting that continued intensive glycaemic control which lowers the HbA1c level brings an equal reduction in microvascular complications (American Diabetes Association, 1998).

The role of better diabetic control (i.e. lowering of the blood-glucose level) in slowing the progression or preventing the onset of diabetic-related complications is not fully understood and to some extent controversial. The Diabetes Control and Complications Trial (DCCT) a prospective study restricted to Type I diabetics, showed a statistically significant risk reduction in the onset and progression of microvascular complications with the reduction in blood glucose level over time. However, there were no statistically significant reductions in cardiovascular complications (DCCT, 1993). The University Group Diabetes Program (UGDP) in 1970 first showed that the lowering of blood-glucose levels with oral antidiabetic drugs (Sulfonylureas) may in fact lead to an increase in cardiovascular events. Unlike the UGPD study, the UKPDS did not find increased levels of cardiovascular events with use of oral antidiabetic drugs.

Mash (2010) indicated that certain lifestyle factors e.g. smoking, alcohol consumption and psychological stress, may have an impact on diabetic control and complications.

A recent systematic review has indicated that the onset of type II diabetes is higher amongst smokers, although paradoxically cessation of smoking also tends to increase the risk of type II diabetes relative to those who have never smoked (Sattar, Sorensen, Taylor, Morris and Munafo, 2015). This research found the same levels of smoking prevalence in cases and controls. The Body Mass Index (BMI) of the study participants was not associated with the presentation of treatment-requiring diabetic retinopathy.

Type II diabetes tends to occur concurrently with other metabolic conditions such as hypertension and dyslipidaemia. Ciulla *et al.* (2003) in their review, indicated that many studies have demonstrated the role of these metabolic conditions combined with elevated blood-glucose levels in the pathophysiology of diabetic retinal changes.

The study participants had a high prevalence of hypertension (89.2%) and a moderate prevalence of dyslipidaemia (22.5%). However, unlike the research conducted by Ciulla *et al.* (2003) these associated metabolic disorders had no relationship with the presence of treatment-requiring diabetic retinopathy. The high proportion of hypertensive co-morbidity may have influenced the grade of retinopathy of fundal images, as hypertension also lead to retinal vasculature changes which may mimic diabetic retinopathy changes and should be included as a limitation. This was the scenario in the Hoorn Study (van Leiden *et al.,* 2003) where hypertension was found to be associated with the onset of diabetic retinopathy, and was considered a confounder. Mehlsen *et al.* (2011) found that although diastolic blood pressure was associated with the presentation of treatment-requiring diabetic retinopathy, this was not statistically significant. An additional limitation to this study was the omission of the clinical measurement of hypertension per participant. The folder review was merely concerned with the presence of anti-hypertensive treatment and not the clinical measurement thereof. The clinical measurement of hypertension might have had an impact on the overall algorithm due to the close relationship between hypertensive and diabetic control.

The study also sought to develop an algorithm for prioritising those most at risk of developing treatment requiring diabetic retinopathy. The most important parameter would be sensitivity, as the follow up fundal photography of those prioritised would be to establish if those identified as being at risk of diabetic retinopathy actually do have the condition. The highest sensitivity with the use of the algorithm was obtained by combining patients on anti- diabetic treatment for more than five years, insulin dependent and blood-glucose level of more than 8 mmol.L. The sensitivity level (61.2%) would still miss four out of ten patients presenting with treatment-requiring diabetic retinopathy and is thus not recommended at this stage as an effective pre-screening tool. Mehlsen *et al.* (2011) postulates that the algorithm should make use of only a select bunch of clinical markers to lessen the complexity and increase the uptake thereof. Further investigation will be needed to evaluate this process and further identify factors that would define a sub-group with extreme accuracy.

CONCLUSION AND RECOMMENDATIONS

The findings indicate that a sub-set of patients attending the DRS programme in the Klipfontein and Mitchells Plain Sub-Districts have a greater likelihood of presenting with treatment-requiring diabetic retinopathy. However, the sensitivity of an algorithm incorporating these risk factors as a pre-screening tool amongst the study participants is not sufficient for it to be recommended as a screening tool.

The surge in diabetes with the subsequent increase incidence of diabetic retinopathy (especially in the working-age population) will add pressure to the current eye care services rendered in Cape Town. Current diabetic eye care guidelines insist on annual fundal imagery, especially in resource-scarce countries where secondary prevention is stressed and should not be compromised. However, presently we are still struggling to clear the backlog of diabetics who have never undergone a fundal examination, compounded by increases in newly diagnosed diabetics. This necessitates further evaluation of how to use the existing resources as effectively as possible.

Further investigation of the accuracy of the algorithm can be conducted at clinical level, and from there alterations to the algorithm may be made to increase the sensitivity of clinical markers. Using the approach developed by Aspelund *et al.* (2011) research could also investigate the possibility of extending the DRS interval based on the individual risk factors of the diabetic.

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APPENDICES

INFORMATION SHEET

Project Title: Factors associated with diabetic retinopathy requiring treatment on fundal photography in participants of the Cape Town Diabetic Retinopathy Screening programme.

What is this study about?

This is a research project being conducted by Mr HG Alexander at the University of the Western Cape. We are inviting you to participate in this research project because you are diabetic patient receiving medical care at a community health centre within the circumscribed study area. The purpose of this research project is to ascertain if there is any notable differences amongst the characteristic of a diabetic patient who presents with treatment-requiring diabetic retinopathy and those who present with non-treatment-requiring diabetic retinopathy.

What will I be asked to do if I agree to participate?

You will be asked to undergo retinal camera imaging which will coincide with your diabetic visit at your attending clinic. Thereafter an interviewer will ask you some general information with regards to your overall health and well-being. The other relevant study information will be sourced from your clinical folder.

Would my participation in this study be kept confidential?

We will do our best to keep your personal information confidential. To help protect your confidentiality, a code will be assigned to each patient thus keeping your particulars confidential. The review of the folders will be conducted on-site with permission from the relevant facility manager.

What are the risks of this research?

There are no risks associated with participating in this research project beyond the usual care you receive at the clinic.

What are the benefits of this research?

The benefits to you is to have the back of your eye photographed and evaluated by a professional grader, and include the necessary follow up care. The study forms part of the

current diabetic retinal screening program conducted at your facility, and the information obtained will lead to future improvements.

Do I have to be in this research and may I stop participating at any time?

Your participation in this research is completely voluntary. You may choose not to take part at all. If you decide to participate in this research, you may stop participating at any time. If you decide not to participate in this study or if you stop participating at any time, you will not be penalized or lose any benefits to which you otherwise qualify

Is any assistance available if I am negatively affected by participating in this study?

If you feel that partaking in the study had a negative impact either socially, emotionally and/or physically then assistance will be provided from the relevant facility managers.

What if I have questions?

This research is being conducted by, Mr HG Alexander from the University of the Western Cape. If you have any questions about the research study itself, please contact myself at:

The Woodstock Hospital (Eye Clinic)

Mountain Road

Woodstock

7925

Tel: (021) 447 0007

Email: henry.george.alexander@gmail.com

Should you have any questions regarding this study and your rights as a research participant or if you wish to report any problems you have experienced related to the study, please contact:

Director:

Prof Helene Schneider

School of Public Health

University of the Western Cape

Private Bag X17

Bellville 7535

hschneider@uwc.ac.za

Dean of the Faculty of Community and Health Sciences:

Prof Jose Frantz

University of the Western Cape

Private Bag X17

Bellville 7535

chs-deansoffice@uwc.ac.za

UNIVERSITY of the WESTERN CAPE

OFFICE OF THE DEAN

DEPARTMENT OF RESEARCH DEVELOPMENT

08 June 2015

To Whom It May Concern

I hereby certify that the Senate Research Committee of the University of the Western Cape approved the methodology and ethics of the following research project by:
Mr HG Alexander (School of Public Health)

Research Project:	Factors associated with diabetic retinopathy requiring treatment based on fundal photography in participants of the Cape Town Retinal Screening Programme.
Registration no:	15/4/35

Any amendments, extension or other modifications to the protocol must be submitted to the Ethics Committee for approval.

The Committee must be informed of any serious adverse event and/or termination of the study.

Ms Patricia Josias
Research Ethics Committee Office
University of the Western Cape

FIRST NAME	SURNAME	GENDER
ID	AGE	CHC
TEL NO	ADDRESS	

Place Clinic Sticker here

OCULAR HISTORY		
	DIABETES TYPE OF TREATMENT	DIAB ETE
CO-MORBIDITIES	ORAL SUPPLEMENTS	
SMOKING NO YES ….NUMBER OF PACKS PER DAY		
ALCOHOL CONSUMPTION …… DRINKS PER WEEK		
DATE OF LAST FUNDUS PHOTOGRAPH	DRS ATTENDANCE HISTORY IN THE PAST FIVE YEARS	

CLINICAL MEASUREMENT			CLINICIAN:
HEIGHT	WIEGHT	BP	WASIT CIRCUMFERENCE
BLOOD GLUCOSE	TODAY	6 MONTH AVERAGE	ONE YEAR AGO
MOST RECENT HBA1C	PEDAL EXAM		

EYE EXAMINATION		CLINICIAN:
HABITUAL VISUAL ACUITY	R	L
PINHOLE VISUAL ACUITY	R	L
INTRA OCULAR PRESSURE	R	L
RED REFLEX PRESENT	R	L
PUPIL REFLEX	R	L

DIABETIC RETINOPATHY SCREEN-ING	RIGHT EYE	LEFT EYE GRAD	FOLLOW UP CARE	
NO DIABETIC RETINOPATHY			ANNUAL REVIEW	
MILD/ MODERATE DIABETIC RETINOPATHY			6 MONTHS REVIEW	
SEVERE DIABETIC RETINOPATHY			REFER TO OPTOMETRIST	
PROLIFERATIVE DIABETIC RETINOPAHTY			REFER FOR TREATMENT	
MACULAR INVOLVEMENT				

I ……. HEREBY DECLARE THAT THE NATURE OF THE STUDY WAS CLEARLY EXPLAINED TO ME, AND THAT I CONSENT TO PARTAKING IN THIS STUDY.