CORNEAL DONATIONS IN SOUTH AFRICA: A 15-YEAR REVIEW

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I, Nicholas York, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university. This work has not been published prior to registration to the abovementioned degree.

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Date: 4/3/2017
Abstract

**Background:**
Corneal pathology is one of the leading causes of preventible blindness in South Africa. A corneal transplant procedure can restore, or significantly improve vision in most of these patients. In current South African clinical practice however, there is a gross shortage of corneal tissue available to ophthalmologists to perform these procedures. There is little published data on corneal donations in South Africa describing the magnitude of the current problem.

**Objectives:**
To describe trends in the number of corneal donors per year, the number of corneal transplants performed each year, the origin of corneal donors, the allocation of corneas to the public or private sector and the demographics of corneal donors in South Africa.

**Methods:**
A retrospective review of all corneal donations made to South African eye banks during a 15-year study period from 1 January 2002 to 31 December 2016.

**Results:**
A progressive decline in corneal donors was found over the study period, from 565 donors per year in 2002 to 89 donors in 2016. As a direct result, there has been an 85.5% decrease in the number of corneal transplants performed per year using locally donated corneas, from 1049 in 2002 to 152 in 2016. 48.8% of donors originated from mortuaries, 39% from private hospitals and 12.2% from government hospitals. Donors originating from mortuaries showed the most significant declines over the 15 year period, decreasing by 94.8%. 79.3% of donated corneas were allocated to the private sector while 21.7% were allocated to the public sector. Demographic data showed that 69.1% of donors were male, while 30.9% were female. 77.2% were white, 14.0% coloured, 6.3% black and 2.5% Indian/Asian. Age of donors demonstrated a bimodal peak, at 25 and 55 years.

**Conclusion:**
The number of corneal donations in South Africa has markedly declined, causing the burden of corneal disease requiring corneal transplantation to continually rise. This study describes the magnitude and trends of the current problem in South Africa. The demographic data has identified certain low donor rate groups within the South African population, where there are possible cultural and other objections to corneal donation. These should serve as a major focus of future research and initiatives aimed at reversing the current trends.
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Abbreviations

CTE: Centre for Tissue Engineering
DALK: Deep Anterior Lamellar Keratoplasty
DALY: Disability Adjusted Life Years
DMEK: Descemets Membrane Endothelial Keratoplasty
DoH: Department of Health
DSAEK: Descemets Stripping Automated Endothelial Keratoplasty
EBAA: Eye Bank Association of America
HIV: Human Immunodeficiency Virus
ICU: Intensive Care Units
KZN: KwaZulu Natal
ODF: Organ Donor Foundation
ODR: Organ Donation Rate
ONT: Organizacion Nacional de Transplantes
(National Transplant Organization of Spain)
PKP: Penetrating Keratoplasty
PMP: Per Million Population
POPI: Protection Of Public Information Act
SA: South Africa
SAPS: South African Police Services
SATiBA: South African Tissue Banking Association
TDC’s: Transplant Donor Coordinators
UK: United Kingdom
USA: United States of America
CHAPTER 1: INTRODUCTION & LITERATURE REVIEW

1.1 INTRODUCTION

Corneal pathology is one of the leading causes of preventable blindness in both adult and paediatric populations in South Africa (SA) and around the globe. A corneal transplant procedure (penetrating or lamellar keratoplasty) can restore, or significantly improve the vision in the majority of affected patients. Keratoplasty is a surgical technique whereby diseased cornea is removed and replaced with donor corneal graft tissue.

In current South African clinical practice, there is a major shortage of corneal graft tissue available to both the private and public sector. Private ophthalmologists have to a large extent compensated for this demand-supply inequity by importing donor corneas from countries such as the United States of America (USA) for example, where local supply of corneal tissue far exceeds their national demands. For the vast majority of South Africans however, the cost of these imported corneas (R20 000 – R25 000 per graft) makes them unaffordable. As a result, patients requiring corneal transplant procedures are placed on long waiting lists, for months to years before a cornea becomes available. This prolongs visual disability in patients with a potentially treatable cause. In some, the delays result in sight becoming permanently and irrevocably lost.

There is little data published on the numbers of locally harvested corneal graft donations being made available to private and public sector ophthalmologists in South Africa. A scientific letter on corneal donations at the Gauteng Cornea and Eye Bank reported that the numbers of corneal graft donations in Gauteng had steadily declined between 1998 and 2008. An editorial by Meyer, without expanding on the exact year-to-year figures, described a 41% decline in national corneal donations in South Africa over a four-year period from 2003 to 2006. The reasons given for the progressive decline in South African corneal donations were threefold: legislative changes in South African mortuaries, rising levels of infectious diseases in donors and lack of public awareness.

In early 2007, the South African national waiting list for corneal transplants totaled 1738 adults and 146 children. This figure, albeit a large one, is outdated and does not take into account the fact that many eye clinics around South Africa have stopped keeping waiting lists altogether, due to the extreme scarcity of corneal tissue available to them. This is especially the case in remote areas, far from the larger South African metropoles.
1.2 LITERATURE REVIEW

BURDEN OF CORNEAL BLINDNESS GLOBALLY AND IN SOUTH AFRICA

Global estimates of visual impairment published by the World Health Organization in 2010 indicate that there are 285 million visually impaired people around the globe, and roughly 39 million who are blind.\[^{1,4}\] Corneal pathology accounts for approximately 12% of blindness globally, with an estimated 4.9 million corneal blind persons worldwide.\[^{5}\] In most developing countries, where poor socioeconomic circumstances play an important role in corneal diseases such as trachoma, xerophthalmia, onchocerciasis (river blindness), and infective keratitis, corneal blindness is proportionately higher.\[^{6,7}\] A study of African countries estimated corneal causation of blindness of up to 30% in certain regions.\[^{8}\] In South Africa, the impact of these developing country illnesses is much less, and a population-based study by Cockburn from Cape Town, estimated corneal causation of blindness to be more closely aligned with developed country estimates at 3-4%.\[^{9}\]

Corneal pathology plays a more significant role in the paediatric population, with global estimates of corneal causation of blindness reaching 20%.\[^{4}\] O’Sullivan studied the aetiology of blindness in children at South African blind schools and found that 11% was corneal in origin.\[^{10}\] Corneal blindness tends to occur at a much younger age than other major causes of preventable blindness such as cataracts and glaucoma.\[^{11}\] The Disability Adjusted Life Years (DALY’s) of corneal blindness are thus significantly higher.\[^{4,12}\] Dandona et al argue that because of the higher DALY’s with corneal disease, ophthalmic public health initiatives should place more emphasis on treating or preventing these disorders, rather than the current systems approach of placing highest emphasis on cataracts, which is typically a disease of the elderly.\[^{9}\]

CORNEAL TRANSPLANTATION

The first successful corneal transplant procedure was a full thickness, or penetrating keratoplasty, performed in 1905 by Dr Edward Zirm on a farm laborer in Czechoslovakia who had opaque corneas following a previous chemical injury.\[^{13}\] Over the next hundred years, penetrating keratoplasty (PKP) was established as the gold standard for corneal transplant procedures.\[^{14}\] The cornea is an immunologically privileged and avascular tissue, and corneal transplantation has thus proven to be much more successful than other solid organ transplants. PKP has an overall graft survival of 90% reported at 5 years for first time grafts and 53% for re-grafts.\[^{15}\] A study published by Wagoner on visual outcomes following full thickness corneal transplantation, demonstrated that PKP resulted in improvement in vision in 82.4% of eyes.\[^{16}\]

The benefit of PKP is that it is a ‘one-size-fits-all’ procedure, which can theoretically be performed on any eye with impaired vision due to corneal pathology.\[^{14}\] Whether the pathology arises from the endothelium, the stroma, or involves all the layers of the cornea, a penetrating keratoplasty remains a suitable procedure. Penetrating keratoplasty is however not without its shortfalls. Major post-operative complications include post-PKP astigmatism, wound dehiscence, allograft rejection,
Over the last decade there has been a major shift from PKP towards partial thickness, or lamellar corneal transplant procedures. Lamellar keratoplasty procedures such as Deep Anterior Lamellar Keratoplasty (DALK), Descemets Stripping Automated Endothelial Keratoplasty (DSAEK) and Descemets Membrane Endothelial Keratoplasty (DMEK) are targeted at specifically replacing only the diseased layers of the cornea, rather than the entire full thickness cornea.

DALK is beginning to replace penetrating keratoplasty in diseases of the anterior cornea (epithelium, Bowman’s layer and stroma), where the endothelium is uninvolved. The benefits of performing DALK rather than PKP include lower risk of graft rejection, less endothelial cell loss and greater long term predicted graft survival (49 years with DALK versus 17.3 years with PKP).

DSAEK has become the procedure of choice for disorders causing corneal endothelial dysfunction. The advantages of DSAEK over PKP include reduced post-operative astigmatism, lower rates of wound dehiscence, avoidance of suture related complications and faster visual rehabilitation.

DMEK is a newer surgical technique, whereby only the Descemets membrane and endothelium are transplanted. The advantages of DMEK include improved visual outcomes, faster visual rehabilitation and a reduced rate of graft rejection. Because there is no stromal tissue being transplanted in this procedure the antigenic stimulus in the graft is greatly reduced and thus the rate of allograft rejection in DMEK is 20 times lower than that in PKP.

**INDICATIONS FOR CORNEAL TRANSPLANTATION**

General indications for corneal transplantation can be divided into four broad groups:

1. Optical keratoplasty is aimed at improving or restoring vision in a patient with a variety of corneal diseases such as keratoconus, corneal dystrophies, corneal scarring and pseudophakic bullous keratopathy.
2. Tectonic keratoplasty is aimed at restoring or maintaining the structural integrity of the cornea, for example in an eye with an infectious or inflammatory corneal melt.
3. Therapeutic keratoplasty is aimed at removing the entire infectious focus in eyes with a recalcitrant infective keratitis.
4. Cosmetic keratoplasty is aimed at improving cosmesis in a blind eye with an unsightly scarred or opaque cornea, but is seldom performed.

In 2016, a survey of Corneal Transplantation in 148 countries, described the most common indications for corneal transplantation as being Fuchs endothelial dystrophy (39%), Keratoconus (27%) and sequelae of infectious keratitis (20%). In South Africa the most common indications for keratoplasty include keratoconus (47%), corneal scarring (28%) and pseudophakic bullous keratopathy (10%).

[14,16,17,18]
CORNEAL DONATIONS IN SOUTH AFRICA: THE SHORTAGE OF CORNEAL TISSUE AND THE PAUCITY OF AVAILABLE PUBLISHED DATA

There have been only two published reports on corneal donations in South Africa in the last 20 years. In 2007, an editorial by Meyer described a 41% decline in the number of locally harvested corneas in South Africa over a four-year period, from 2003 to 2006.[2] This was attributed to numerous factors including legislative changes in forensic mortuaries in 2006, rising levels of HIV and other infections excluding potential donors, and a lack of public awareness around organ donation. It also reported that the South African national corneal transplant waiting list in 2007 consisted of 1738 adults and 146 children.

A scientific letter published in 2009 by Makgotloe on corneal donations in Gauteng province, described that the number of corneal donations in Gauteng had steadily increased from 137 in 1998 to 176 in 2005. However, in a similar trend to that described by Meyer, corneal donations in Gauteng then followed a state of steady and significant decline of more than 65% over the following three years. The number of donations per year dropped to 114 in 2006, 93 in 2007 and by 2008 only 57 corneas were donated.[3] Makgotloe also described the demographic data of corneal donors at Gauteng eye bank. White donors accounted for 96.8%, while black, Asian and mixed race donors accounted for 1.6%, 1.2% and 0.4% respectively. The majority of donors came from mortuaries (51.8%) and private hospitals (35%). 10% originated from public sector hospitals.

To the best of my knowledge, there is no other published data on corneal donations in South Africa.

PUBLIC ATTITUDES OF SOUTH AFRICANS TOWARDS ORGAN DONATION

In 1993, Pike published an article investigating the attitudes of South Africans from different ethnic groups towards organ donation.[27] There was a general perception among healthcare workers that black South Africans were less likely to consent to donation of their own, or their relative’s organs, due to various cultural beliefs and superstitions. Pike interviewed 825 urban black, 625 rural black and 1299 urban white South Africans. 76% of the urban black, 84% of rural black and 89% of the urban white respondents indicated that they would be willing to donate their organs. This to some extent dispels common misconceptions about the attitudes of black South Africans towards organ donation in general.

This was not the case however with regards to the prospect of corneal donations. Only 23% of black respondents said that they would be willing to donate their corneas, compared to a significantly higher 69% and 70%, who would be willing to donate their kidneys and hearts respectively. This highlights the fact that cultural beliefs and superstitions may play a more significant role in the donation of corneas, as opposed to donation of solid organs. These potential barriers would need to more adequately defined and specifically addressed in any programs aimed at improving uptake of corneal donation in South Africa.
All race groups were less comfortable with the idea of consenting to the donation of the organs of one of their close relatives. Most respondents felt that the principal donor, prior to their demise, should preferably be the one responsible for making this decision, and not the family member after death. Most respondents across all race groups felt that the race of both the donor and the recipient was irrelevant in organ donation.

**EYE BANKING**

**A) HISTORY OF EYE BANKING GLOBALLY**

An eye bank is an organization that acquires, prepares, evaluates, stores and distributes donated corneas for use in corneal transplantation.

From the time of the first corneal transplant by Edward Zirm in 1905, until the mid-1930’s, the only source of corneal tissue was from living donors who had undergone an enucleation for pathology involving only the posterior segment of the eye. There were no means available for storage of these corneas and prevention of cell death and thus transplantation had to be performed immediately after enucleation. In 1937, a Russian ophthalmologist, Vladimir Filatov, discovered that cadaver corneal tissue could be stored in a moisture chamber at 4°C for 24-36 hours post mortem. This means of storing corneal tissue, albeit for a short time period was the initiating event, that would later develop into eye banking.

A scientific breakthrough in the 1970’s saw the development of the McKarey-Kaufman tissue medium, which allowed corneas to be stored at 4°C for up to 4 days. Further advancements in tissue preservation saw the development of Organ Culture Medium, which could safely store corneas at 34°C for up to 35 days. Later refinements led to the production of commercially available storage media such as Optisol, which allow a simple and safe storage solution at 4°C for 14-21 days. This meant that corneal transplantation no longer needed to be performed as an emergency procedure, but could now be scheduled on a semi-elective basis, with better preparation of the recipient, analysis of the donor cornea and availability of appropriate expertise during working hours.

The worlds first Eye Bank was founded in 1944 in New York by Richard Townley Paton. The aim of the eye bank was to collect, store and then distribute corneal tissue to qualified ophthalmic surgeons. Over the next 15 years, there was an ever-increasing number of eye banks being established across the United States of America (USA). In 1961, the Eye Bank Association of America (EBAA) was established in order to better co-ordinate and administer the efforts of all of the American Eye Banks. The EBAA now consists of 71 USA-based and 10 international-affiliated eye banks. The most recent EBAA statistical report shows that 79,304 corneas were supplied for keratoplasty in 2015 alone. 65% of these were distributed to corneal surgeons within the USA, while 35% were exported internationally to countries including South Africa. Numerous other similar eye bank Associations have subsequently been established around the globe.
B) HISTORY OF EYE BANKING IN SOUTH AFRICA

The first South African eye bank, the Eye Bank Foundation of South Africa was established in Cape Town in 1975. Over the following 30 years, additional eye banks were opened in Gauteng, Pretoria, Port Elizabeth and KwaZulu Natal, so that by 2003, there were five operational eye banks in South Africa. Unfortunately as a result of increasingly strict legislature and financial difficulties, both the Port Elizabeth eye bank and the Pretoria eye bank closed operations at the end of 2010, leaving only three remaining banks. In 2011 however, the Centre for Tissue Engineering in Pretoria, an organization already functioning as a tissue bank for skin, bone, tendons and heart valves, started harvesting and distributing corneas as well. Thus in 2017, there are essentially four eye banks still operating in South Africa.

MECHANISMS TO INCREASE ORGAN DONATIONS RATES

A) LEGISLATIVE CHANGES

Legislature and national policies regarding organ and tissue donation vary widely around the globe. In broad terms however, two main systems have been adopted, namely an ‘opt-in’ system and an ‘opt-out’ system. An ‘opt-in’ system means that citizens have to make an active decision prior to death that they would like to be an organ donor upon their demise. This decision can be made in various forms, such as signing up to an organ donor registry, informing family members, or in the form of a living will. An ‘opt-out’ system however, means that consent to organ donation is presumed, unless a specific request has been made known prior to death, that the person does not wish to become an organ donor on their demise. This decision can be made known by various similar means to those described above.

A large-scale review published by a group from Nottingham University in 2014 compared organ donation rates in 48 countries over a 13-year period, from 2000 to 2012. They noted that organ donation rates were significantly higher in countries that adopted an ‘opt-out’ organ donation system. After legislative changes implemented in 2015, Wales was the first country in the United Kingdom (UK) to adopt a variation of the ‘opt-out’ system, termed a ‘soft opt-out’ system. The main difference is that the family is still consulted in the final decision-making after death, and if the deceased had expressed that he or she did not wish to be an organ donor, then the family can opt-out on their behalf. Early reports suggest a 24% increase in transplants since the introduction of this system. In June 2016, the British Medical Association, representing 150 000 doctors in the UK, voted in favour of a referendum to lobby the British government to change the legislature to an opt-out organ donation system for the entire UK.

B) ORGANIZATION AND PROFESSIONALIZATION OF ORGAN DONATION

Organ donation rates are expressed as donors per million population (pmp). World leaders in organ donation such as Spain, have organ donation rates of >30 pmp, while other developed countries such as the USA, France and Italy have rates between 20 and 30. The UK and Germany have lower rates in the mid teens. South Africa by stark contrast has one of the lowest organ donation rates in the
world, at just 2-3 pmp.\[39\] Legislative change to an opt-out system alone however, does not necessarily guarantee an increase in organ donations. Singapore for example, is the only country with an enforced ‘opt-out’ system. In this system if a person has not explicitly opted out of organ donation prior to being declared brain dead, they are presumed to consent to organ donation, and their family cannot override this consent after their demise. Although this legislative change resulted in a 50-fold increase in the number potential donors, the actual donor rate has remained relatively low at 7-9 pmp.\[40\] This is because of lack of an organized transplant program in hospitals to convert potential donors into actual donors.

Thus, while legislative changes do increase the numbers of potential donors, the conversion rate to increasing the number of actual donors relies on various other factors, which have been the major focus of the highly effective ‘Spanish Model’ of organ donation described below. Spain, in addition to utilizing a soft opt-out system, established a highly efficient National Transplant Organization (ONT) in 1989. This organization, which is run by the Spanish health department, ensures a high conversion rate of potential donors into actual donors. The ONT has achieved this by introducing the role of Transplant Donor Coordinators (TDC’s) into every hospital in Spain. The TDC’s are mostly ICU physicians, and more recently nursing sisters. They undergo special training and play a vital role in promoting organ donation within their hospital by identifying potential donors, discussing organ donation with family members, and referring the organ donor to a transplant team after brain death. The Spanish Model also relies on a stringent Quality Assurance Program, which regularly audits organ donation practices, in order to identify possible areas for improvement.\[38\] These strategies have proven highly effective in pivoting Spain to the position of world leader in organ donation.

1.3 OBJECTIVES

The main objectives of this study are to obtain and analyze South African corneal donor data over a 15-year period from 1 January 2002 to 31 December 2016, describing:

i. The trends in numbers of corneal donors per year
ii. The trends in corneal transplants performed per year using locally donated corneas
iii. The origin of corneal donors, whether from public hospitals, private hospitals or mortuaries
iv. The allocations of corneal graft tissue, whether to the public or private health care sectors
v. The demographics of corneal donors in South Africa

1.4 JUSTIFICATION FOR THE STUDY

The first step in the process of reversing the current situation of declining corneal donations in South Africa, is to publish current data and highlight trends in corneal donations, both nationally and at the level of the individual eye banks. Once this information is obtained, it can be presented to government and eye bank policymakers and used to motivate for new strategies and legislative changes to increase
corneal donations in South Africa. The data on the demographics of corneal donors will identify low donor rate groups, which should be the focus of future research and initiatives to increase donations and relieve the current shortage of corneal tissue experienced in South African clinical practice.

1.5 REFERENCES

Chapter 2: Publication-ready Manuscript

Corneal donations in South Africa: A 15-year review

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Abstract

Background:
Corneal pathology is one of the leading causes of preventible blindness in South Africa. A corneal transplant procedure can restore, or significantly improve vision in most of these patients. In current South African clinical practice however, there is a gross shortage of corneal tissue available to ophthalmologists to perform these procedures. There is little published data on corneal donations in South Africa describing the magnitude of the current problem.

Objectives:
To describe trends in the number of corneal donors per year, the number of corneal transplants performed each year, the origin of corneal donors, the allocation of corneas to the public or private sector and the demographics of corneal donors in South Africa.

Methods:
A retrospective review of all corneal donations made to South African eye banks during a 15-year study period from 1 January 2002 to 31 December 2016.

Results:
A progressive year-on-year decline in corneal donors was found over the study period, from 565 donors per year in 2002 to 89 donors in 2016. As a direct result, there has been an 85.5% decrease in the number of corneal transplants performed per year using locally donated corneas, from 1049 in 2002 to 152 in 2016. 48.8% of donors originated from mortuaries, 39% from private hospitals and 12.2% from government hospitals. Donors originating from mortuaries showed the most...
significant declines over the 15 year period, decreasing by 94.8%. 79.3% of donated corneas were allocated to the private sector while 21.7% were allocated to the public sector. Demographic data showed that 69.1% of donors were male, while 30.9% were female. 77.2% were white, 14.0% coloured, 6.3% black and 2.5% Indian/Asian. Age of donors demonstrated a bimodal peak, at 25 and 55 years.

**Conclusion:**
The number of corneal donations in South Africa has markedly declined, causing the burden of corneal disease requiring corneal transplantation to continually rise. This study describes the magnitude and trends of the current problem in South Africa. The demographic data has identified certain low donor rate groups within the South African population, where there are possible cultural and other objections to corneal donation. These should serve as a major focus of future research and initiatives aimed at reversing the current trends.

**Keywords:**
Corneal donations, South Africa
Background
Corneal pathology is one of the leading causes of preventable blindness around the globe, accounting for approximately 4% of preventable blindness worldwide.\cite{1,2} Corneal disease is the cause of visual loss in 11% of blind or severely visually-impaired children and 4% of blind adults in South Africa (SA).\cite{3,4} A corneal transplant procedure (penetrating or lamellar keratoplasty) can restore or significantly improve vision in the majority of affected patients. Keratoplasty is a surgical procedure whereby diseased cornea is removed and replaced with donor corneal graft tissue. Modern advances in surgical techniques and surgeon expertise have resulted in continual improvements in visual outcomes with these procedures.\cite{5,6,7}

In South African clinical practice, there is a major shortage of corneal graft tissue available to both the private and public sector. Private sector ophthalmologists have, to a large extent, compensated for this demand-supply inequity by importing donor corneas from countries such as the United States of America for example, where local supply of corneal tissue far exceeds their national demands.\cite{8} For the vast majority of South Africans however, the cost of these imported corneas (R20 000 – R25 000 per graft) makes them unaffordable.\cite{9} As a result, patients requiring corneal transplant procedures are placed on long waiting lists, for months to years before a cornea becomes available.\cite{9} This only prolongs visual disability in patients with a potentially treatable cause. In some, these delays result in sight becoming permanently and irrevocably lost.

Published data on the numbers of locally harvested corneal graft donations being made available to private and public sector ophthalmologists in South Africa is scarce. A scientific letter on corneal donations at the Gauteng Cornea and Eye Bank reported that the numbers of corneal graft donations in Gauteng had steadily diminished between 1998 and 2008.\cite{10} An editorial written by Meyer, without expanding on the exact year-to-year figures, described a 41% decline in national corneal donations in South Africa over the four-year period from 2003 to 2006.\cite{9} The reasons given for the progressive decline in South African corneal donations were threefold: legislative changes in South African mortuaries, rising levels of infectious diseases in donors and lack of public awareness. The most recent published figure for the South African national corneal transplant waiting list was in 2007, and totaled 1 738 adults and 146 children.\cite{9} This figure, albeit a large one, is outdated and likely a gross underestimate of the current situation. The number of people waiting for corneal transplantation will continue to rise, unless strategies are implemented to reverse these trends.

Objectives
To describe trends in the number of corneal donors per year, the number of corneal transplants performed each year, the origin of corneal donors, the allocation of corneas and the demographics of corneal donors in South Africa.

Methods
A retrospective review was conducted of all corneal donations made to South African eye banks that were operational at any time during the 15-year study period,
from 2002 to 2016. Data collection templates were sent to the directors of the four currently operational South African eye banks, namely the Gauteng Cornea & Eye Bank in Johannesburg, the Eye Bank Foundation of South Africa in Cape Town, the KwaZulu-Natal Cornea & Eye Association in Durban and the Centre for Tissue Engineering (CTE) in Pretoria (which began eye banking in 2012, after the closure of the previously operational Pretoria eye bank in 2010). Data was extracted from the pre-existing databases kept by the various eye bank directors on corneal donations in each of their respective banks. The data collection templates were designed to capture information on the numbers of corneal donors per year, the numbers of corneal transplants performed per year using corneas donated to each of the local eye banks, the origin of corneal donors, the distribution of allocated corneas to the public and private health care sectors and the demographics of corneal donors.

The Pretoria Eye Bank and the Port Elizabeth Goosen Eye Bank both closed operations in 2010. The closure of these two eye banks meant that data available from these institutions was limited only to the number of corneal transplants performed per year using graft donations to these banks. No other information on origin of donors, allocation of grafts or donor demographics was available from these banks.

This study was approved by the Human Research Ethics Committee, Faculty of Health Sciences, University of Cape Town (HREC/REF:883/2014) and conformed to the principles of the 2013 Declaration of Helsinki.\[11\]

Results

There were a total of 3 738 corneal donors nationally in South Africa from 2002-2016 (Table 1). Given the fact that in most cases, each corneal donor is able to donate two corneas, this translated into 6 588 locally-donated corneal grafts being supplied for corneal transplant procedures over the 15 year study period (Table 2). The Gauteng Cornea and Eye Bank supplied 2 530 corneas (38.4%), the Cape Town Eye Bank (Eye Bank Foundation of South Africa) supplied 1 805 corneas (27.4%), the combined efforts of the Pretoria Eyebank from 2002-2010 and the CTE from 2012-2016 (both operating in Pretoria) supplied 1 195 corneas (18.1%), the KZN Cornea and Eye Association supplied 931 corneas (14.1%) and the Port Elizabeth Goosen Eye Bank supplied 127 corneas (2%). 10.5% of the donated corneas were either discarded or donated for research purposes. The main reasons for discarding donated corneas included positive donor virology (HIV, Hepatitis B and C), low endothelial cell count (<2000cells/mm²), damaged or scarred grafts and a positive culture on a swab taken from the graft.
Table 1. Number of corneal donors* per year at the South African eye banks

<table>
<thead>
<tr>
<th>Year</th>
<th>Gauteng†</th>
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<th>Pretoria†</th>
<th>Port Elizabeth†</th>
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<td>681</td>
<td>70</td>
<td>3 738</td>
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</table>

*Note: a corneal donor refers to one deceased individual, with the potential to donate two corneas in the majority of cases.

† Gauteng = Gauteng Cornea and Eye Bank, Cape Town = Eye Bank Foundation of South Africa, KZN = KwaZulu Natal Cornea and Eye Association, Pretoria = Pretoria Eye Bank (2002-2010) and CTE (2012-2016), Port Elizabeth = Port Elizabeth Goosen Eye Bank

‡ Numbers from the Pretoria and Port Elizabeth eye banks from 2002-2010 are estimates of corneal donor numbers per year calculated from available data on number of actual corneal grafts donated to these banks per year and adjusted for a mean of 2 corneal grafts per donor and an average discard rate for donated corneal grafts of 10.5%. The figure of 10.5% is the mean discard rate calculated from data from the Gauteng, Cape Town and KZN eye banks, where more data was available.
**Table 2. Number of corneal transplants per year using corneas donated to the South African eye banks**

<table>
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<th>Year</th>
<th>Gauteng</th>
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<th>KZN</th>
<th>Pretoria</th>
<th>Port Elizabeth</th>
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<tr>
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<td>79</td>
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<tr>
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<td>28</td>
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<tr>
<td>Total</td>
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<td>1 805</td>
<td>931</td>
<td>1 195</td>
<td>127</td>
<td>6 588</td>
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</table>
Trends in numbers of corneal donors per year
The trendline graph of corneal donors nationally (Figure 1) shows a progressive decline in corneal donors from 565 donors in 2002 to 89 donors in 2016, an 84.2% decline over the 15 year study period. The most significant decline occurred in the period from 2005 to 2007, with a 50.9% drop in donor numbers occurring during that 2 year period alone. The trend of progressively decreasing corneal donor numbers was consistent across all of the South African eye banks.

Figure 1. Trendline graph of number of corneal donors per year nationally
Trends in numbers of corneal transplants performed per year, using corneas donated to the South African eye banks

The trends in the number of corneal transplants performed nationally per year, using locally donated corneas, mirrors that found with numbers of corneal donors. The number of transplants per year decreases significantly and progressively (Figure 2), with an 85.5% decrease over the 15 year period, from 1 049 at the start of the study in 2002, to just 152 at the end of the study in 2016. As with the drop in corneal donors, the most significant decrease in numbers occurred over the period from 2005 to 2007, with a 45.7% decrease occurring during this time. Again this trend of progressively decreasing numbers of corneal transplants performed per year is consistent across all of the eye banks.

Figure 2. Trendline graph of number of corneal transplants per year nationally using corneas donated to the South African eye banks
Origin of corneal donors
Data on the origin of corneal donors was obtained from the three South African eye banks which were operational for the entire study period, namely the Gauteng, Cape Town and KZN eye banks. Over the 15 year study period, 1 443 donors (48.8%) originated from mortuaries, 1 151 (39%) from private hospitals and 361 (12.2%) from government hospitals. For 32 donors, the origin was unknown. The number of donors per year arising from private hospitals remained fairly constant over the study period, while the number of donors originating from government hospitals appears to be slowly declining (Figure 3). The number of donors originating from mortuaries showed the most significant reductions over the study period, decreasing by 94.8% from 211 donors per year in 2002 to 11 donors per year in 2016 (Figure 3). Again, the most significant declines occurred over the period from 2005 to 2007, with a 69.8% decline occurring during this time.

Figure 3. Trendline graph of origin of corneal donors
Allocation of donated corneas
Of the corneas donated to the Gauteng, Cape Town and KZN eye banks, 4 041 (79.3%) were allocated to private sector patients for corneal transplantation, while 1 058 (20.7%) were allocated to the public sector. The distribution of corneas allocated to public and private sector patients at the Gauteng, Cape Town and KZN eye banks is demonstrated in Figure 4.

Figure 4. Allocation of corneal grafts at three South African eye banks

Demographics of corneal donors
Data on donor demographics was only available from the Gauteng, Cape Town and KZN eyebanks.

a) Gender of corneal donors
2 064 (69.1%) of the donors were male and 923 (30.9%) were female. This approximately 2:1 ratio was consistent across all three eye banks.

b) Race of corneal donors
2 280 (77.2%) of the donors were white, 413 (14.0%) were coloured, 186 (6.3%) were black and 73 (2.5%) were Indian/Asian. White donors made up the largest donor racial group in all three banks, but the proportions of donor races varied substantially (Figure 5). The race was unknown in 35 donors.

Figure 5. Race of corneal donors
c) Age of corneal donors
Of the 2,987 donors at the three major eye banks, 342 (11.7%) were aged between 0-20 years, 957 (32.8%) were aged between 21-40 years, 1,099 (37.7%) were aged between 41-60 years and 519 (17.8%) were aged between 61-80 years. The age was unknown in 70 donors. There was a bimodal peak in age of donors at 25 and 55 years (Figure 6).

Figure 6. Age distribution of corneal donors

Discussion
This study highlights the alarming trend of progressively decreasing numbers of corneal donors in South Africa over the 15 year period. The rapid decline in numbers which occurred between 2005 and 2008 coincides with a time of legislative change affecting South African forensic mortuaries. Prior to 2006, the South African Police Services (SAPS) controlled and managed the forensic mortuaries. Eye bank directors had liberal access to information on deceased persons in the mortuaries and were thus able to easily identify potential donors and contact their next of kin. This made mortuaries the main source of corneal donors at the time. In 2006 however, changes in legislation shifted the governance of the forensic mortuaries from the SAPS to the Department of Health (DOH). The new legislation, with good intention, placed high emphasis on ethical considerations and confidentiality of deceased individuals at the forensic mortuaries. As a consequence of this, access to information on potential donors from the mortuaries was dramatically restricted. In addition, new protocols were instituted in mortuaries, which stipulated that telephonic consent from family members was no longer sufficient, and that written consent would be required from a family member who had identified the deceased in person. Given the fact that the time from death to the harvesting of corneas should ideally be within 12 hours, this was very seldom possible. The result was a rapid fall in donors originating from the forensic mortuaries from 2006 onwards. By 2007, this source of corneal donors had fallen to levels below that of donors originating from private hospitals, and these numbers continued to decline throughout the study period.
The corneal donors originating from private and government hospitals were individuals who were either registered organ donors, or whose family members had consented to their organ donation after brain death had been declared. Transplant coordinators liaise with teams to harvest solid organs and other tissues and contact the relevant eye bank to harvest the corneas. While the number of corneal donors originating from private hospitals has remained fairly constant throughout the 15-year study period, and currently makes up the highest source of corneal donors, the actual numbers of donors remain low. The numbers of donors originating from government hospitals has always been low and has progressively decreased over the study period. Poor public awareness of organ donation, cultural issues regarding organ donation, high HIV and Hepatitis prevalence and poor education and ‘buy-in’ of medical personnel toward referral of potential donors to transplant co-ordinators, have all contributed to the low numbers of corneal donors in our government hospitals.[9, 10, 12] In addition, by global standards, South Africa has a very limited national organ transplant co-ordination program and little government support and funding towards organ donation.[13, 14] Therefore only a very small proportion of patients dying in South African government hospitals become organ donors.

More than two thirds of donated corneas are allocated to the private sector at all three of the major eye banks, even though there is much greater demand for corneas in the public sector. The reasons for this are two-fold. First, there is no current national system for equitable distribution of corneas between public and private healthcare sectors. At present, most of the eye banks treat each private practice ophthalmologist and each public sector ophthalmology department as individual practitioners and attempt to evenly distribute the corneas amongst all of these practitioners. Because there are many more private ophthalmologists than public ophthalmology departments, this system is heavily skewed in favour of the private sector.[15] The second reason is financial. Eye banks are non-profit organisations, whose sources of income to cover running costs and salaries arise from donations and remuneration for corneal tissue supplied. Thus while private sector patients are able to pay for corneal tissue through medical aid funds or personal finances, public health sector ophthalmology departments have very limited budgets available to pay for corneal graft tissue and a much slower turnaround time for payments.[10]

There was an approximately 2:1 male preponderance in corneal donors. As 48.8% of donors originated from forensic mortuaries, a large proportion would have died from unnatural deaths, such as motor-vehicle related accidents, other accidental deaths, murders or suicides. Males are three times more likely than females to die of an unnatural death in South Africa, especially in the younger age group between 15-29 years.[16] It is unknown whether gender itself influences attitudes towards organ donation in South Africa, and this may be a topic for future research.

White donors made up the highest proportion in all three major eye banks, despite being one of the smaller race groups in South Africa. Conversely, black South Africans, the largest race group comprising 79.2% of our population,[17] accounted for a small fraction of the corneal donor pool. This is likely due to cultural beliefs towards organ donation amongst black South Africans. In a survey on public attitudes towards organ donation in South Africa, Pike found that while up to 70% of black respondents said that they would be willing to donate solid organs, only 23% would be willing to donate their corneas.[12] Cultural beliefs and superstitions may
therefore play an even more significant role in the donation of corneas than in the
donation of other solid organs. The possible cultural barriers towards corneal
donation amongst black South Africans requires further investigation and should be a
key focus point in programs aimed at improving uptake of corneal donations in
South Africa. The low number of Indian/Asian donors is likely due to religious
beliefs. In the Muslim faith for example, there is divided opinion on organ donation,
with some Islamic scholars saying that it is strictly prohibited, whilst others argue
that the act of saving another’s life should make it permissible.[18] The higher
proportion of Indian/Asian donors at the KZN eye bank and of coloured donors at the
Cape Town eye bank are likely a reflection of the differences in racial demographics
in these respective provincial population groups.[17] The bimodal peak in age of
donors at 25 and 55 years reflects the fact that the majority of unnatural causes of
death occur in the age group between 15-29 years, while the majority of natural
causes of death occur in patients over the age of 45.[16]

This study clearly defines the magnitude of the current corneal donor shortage and
the alarming trend of progressively declining corneal donations in South Africa. Our
hope is that this information can be used as a platform on which future strategies
aimed at reversing these trends can be built. One of the main reasons for the marked
decrease in number of corneal donors, has been the legislative changes affecting
South African forensic mortuaries. Negotiations should be opened with the
Department of Health (DoH) as to what measures can be taken to improve the
numbers of corneal donors originating from forensic mortuaries, while still
maintaining ethical principles and complying with the Protection of Public
Information (PoPI) Act. Other legislative changes which could benefit not only
corneal donations, but solid organ donations as well, would be a move from the
current ‘opt-in’ organ donation system, to an ‘opt-out’ system. An ‘opt-out’ system
means that all members of the public are presumed to consent to organ donation,
unless they take an active step to opt-out. A large-scale review published by a group
from Nottingham University in 2014 compared organ donation rates in 48 countries
over a 13-year period, from 2000-2012. They noted that organ donation rates were
significantly higher in countries adopting an ‘opt-out’ system.[19] Wales is the first
country in the UK to shift to an ‘opt-out’ system in 2015, resulting in a 24% increase
in transplants in the first year.[20] In June 2016, the British Medical Association,
representing 150 000 doctors in the UK, voted in favour of a referendum to lobby the
British government to change the legislature to an ‘opt-out’ organ donation system
for the entire UK. Spain is the currently the world leader in organ donations, with an
organ donation rate of more than 30 per million population (pmp),[13] compared to
South Africa’s rate of 2-3 pmp, which is one of the lowest worldwide.[14] The reasons
for the huge success of the ‘Spanish Model’ of organ donation lies not only in their
‘opt-out’ legislation, but more importantly in their highly organized and professional
National Transplant Organization (ONT). This state funded organization, which is
run by the Spanish health department, introduced the role of Transplant Donor
Coordinators (TDC’s) into every hospital in Spain. The TDC’s promote organ
donation within their hospital, identify potential donors, discuss organ donation with
family members, and refer the organ donor to a transplant team after brain death.
Similar strategies could be considered by South African policy-makers.

Already there are promising local initiatives attempting to reverse the current trends.
The Organ Donor Foundation (ODF) was established in 1988, with their primary
mandate being to raise public awareness of organ donation in South Africa. Another important collaboration was inaugurated in September 2015, with the formation of the South African Tissue Bank Association (SATiBA). Its purpose is to unite the previously independantly operating eye banks and the other tissue banks (harvesting other tissues such as bone, skin, marrow and others) together under one umbrella body. The objectives are to improve public awareness, standardise procedural protocols, improve education and training of staff and volunteers, improve electronic data collection and publication of donation statistics and support the individual banks in legal and regulatory matters. Most importantly, it aims to consolidate efforts at lobbying government and key policy makers to implement new strategies, changes in legislature and the prioritization of funding, in order to improve the numbers of corneal and other tissue donations in the future.\cite{21}

**Conclusion**

The number of corneal donations in South Africa has markedly declined and this has been a major contributing factor to the continually rising burden of corneal disease requiring corneal transplantation. This study describes the magnitude and trends of the current problem in South Africa. The demographic data has identified certain low donor rate groups within the South African population, where there are possible cultural and other objections to corneal donation. These should serve as a major focus of future research and initiatives aimed at reversing the current trends.

**Author Contributions**

NJY Conceptualized and designed the study, acquired and interpreted the data and drafted the manuscript. CT made substantial contributions to the design of the study and revised the manuscript critically.

**Acknowledgements**

The eye bank directors Lynne Pickering (Gauteng Cornea and Eye Bank), Sharon Munnik (Eye Bank Foundation of SA), Carol Tonnesen (KZN Cornea and Eye Association), Sandra Venter (Centre for Tissue Engineering), and their staff, in addition to Samantha Nicholls (Organ Donor Foundation) are acknowledged for supplying data on organ donations from databases at their respective organizations.
References

5. Wagoner MD, Gonnahel S, Al-Towerki AE; King Khaleed Eye Specialist Hospital Cornea Transplant Study Group. Outcome of primary adult penetrating keratoplasty in a Saudi Arabian population. Cornea 2009;28(8):882-890. https://dx.doi.org/10.1097/ICO.0b013e31819b00d8


https://dx.doi.org/10.1186/s12916-014-0131-4


APPENDICES

1) DATA COLLECTION TEMPLATES

a) Number of corneal donors per year to your eye bank

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b) Number of corneal transplants per year using corneas donated to your eye bank

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d) Allocation of Corneas

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<tr>
<th>Year</th>
<th>Corneas allocated to private sector patients</th>
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<th>Total Number of Corneas allocated</th>
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e) Gender of Corneal Donors

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f) Race of Corneal Donors

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g) Age of Corneal Donors

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<th>0-10 yrs</th>
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2) DEPARTMENT OF SURGERY RESEARCH COMMITTEE APPROVAL

UNIVERSITY OF CAPE TOWN

Department of Surgery

Departmental Research Committee
Professor Anwar Suleman Mall
J-45 Room Old Main Building, Groote Schuur Hospital, Observatory 7925, South Africa
Tel (021) 406 6168/6239/6227 Fax (021) 448 6461
Email: Anwar.Mall@uct.ac.za

24th November 2014

Dr N York
Department of Surgery
Division of Ophthalmology
Groote Schuur Hospital
University of Cape Town

Dear Dr York,

RE: PROJECT 2014/109

PROJECT TITLE: Corneal graft donations in South Africa: a 5 year review

The above proposal was reviewed by the Department of Surgery Research Committee and I am pleased to inform you that the committee approved the study.

Please use the above project number in all future correspondence.

Yours sincerely

[Signature]

PROFESSOR ANWAR S MALL
CHAIRMAN: RESEARCH COMMITTEE

"OUR MISSION is to be an outstanding teaching and research university, educating for life and addressing the challenges facing our society."
3) ETHICS APPROVAL

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

Room 6G-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 404 7682 • Facsimile [021] 406 6411
Email: hrsi.twema@uct.ac.za
Website: www.health.uct.ac.za/research/humanethics/forms

27 November 2014

HREC REF: 883/2014

Dr C Tinley
Ophthalmology Division
GSH

Dear Dr Tinley

PROJECT TITLE: CORNEAL GRAFT DONATIONS IN SOUTH AFRICA: A 5 YEAR REVIEW
(Masters-candidate: Dr N York)

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

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

Approval is granted for one year until the 30th November 2015.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

(Forms can be found on our website: www.health.uct.ac.za/research/humanethics/forms)

We also acknowledge that Masters student Dr N York is involved in this study.

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

Please quote the HREC reference no in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN ETHICS
Federal Wide Assurance Number: FW00001637
Institutional Review Board (IRB) number: IRB00001938

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.
4) ETHICS RENEWAL WITH CHANGE OF DURATION OF STUDY TO 15 YEARS
5) SOUTH AFRICAN MEDICAL JOURNAL (SAMJ) INSTRUCTIONS TO AUTHORS

Author Guidelines

General article format/layout
Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, which will delay publication.

General:
• Manuscripts must be written in UK English.
• The manuscript must be in Microsoft Word or RTF document format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes).
• Please make your article concise, even if it is below the word limit.
• Qualifications, full affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
• Abbreviations should be spelt out when first used and thereafter used consistently, e.g. ‘intravenous (IV)’ or ‘Department of Health (DoH)’.
• Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dL).
• Litres is denoted with an uppercase L e.g. ‘mL’ for millilitres).
• Units should be preceded by a space (except for % and °C), e.g. ‘40 kg’ and ‘20 cm’ but ‘50%’ and ‘19°C’.
• Please be sure to insert proper symbols e.g. µ not u for micro, α not a for alpha, β not B for beta, etc.
• Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.
• Quotes should be placed in single quotation marks: i.e. The respondent stated: ‘...’
• Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.
• If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the only exception. Please DO NOT use fill, format lines and so on.

Preparation notes by article type

Research

Guideline word limit: 4 000 words

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study
methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text.
Do not replicate data in tables and in text.

Structured abstract
• This should be 250-400 words, with the following recommended headings:
  ◦ **Background:** why the study is being done and how it relates to other published work.
  ◦ **Objectives:** what the study intends to find out
  ◦ **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.
  ◦ **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
  ◦ **Conclusion:** must be supported by the data, include recommendations for further study/actions.
• Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors.
• Do not include any references in the abstracts.

Main article
All articles are to include the following main sections: Introduction/Background, Methods, Results, Discussion, Conclusions.
The following are additional heading or section options that may appear within these:
• **Objectives** (within Introduction/Background): a clear statement of the main aim of the study and the major hypothesis tested or research question posed
• **Design** (within Methods): including factors such as prospective, randomisation, blinding, placebo control, case control, crossover, criterion standards for diagnostic tests, etc.
• **Setting** (within Methods): level of care, e.g. primary, secondary, number of participating centres.
• **Participants** (instead of patients or subjects; within Methods): numbers entering and completing the study, sex, age and any other biological, behavioural, social or cultural factors (e.g. smoking status, socioeconomic group, educational attainment, co-existing disease indicators, etc) that may have an impact on the study results. Clearly define how participants were enrolled, and describe selection and exclusion criteria.
• **Interventions** (within Methods): what, how, when and for how long. Typically for
randomised controlled trials, crossover trials, and before and after studies.
• Main outcome measures (within Methods): those as planned in the protocol, and those ultimately measured. Explain differences, if any.

Results
• Start with description of the population and sample. Include key characteristics of comparison groups.
• Main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks.
• Do not replicate data in tables and in text.
• If presenting mean and standard deviations, specify this clearly. Our house style is to present this as follows:
  • E.g.: The mean (SD) birth weight was 2 500 (1 210) g. Do not use the ± symbol for mean (SD).
• Leave interpretation to the Discussion section. The Results section should just report the findings as per the Methods section.

Discussion
Please ensure that the discussion is concise and follows this overall structure – subheadings are not needed:
• Statement of principal findings
• Strengths and weaknesses of the study
• Contribution to the body of knowledge
• Strengths and weaknesses in relation to other studies
• The meaning of the study – e.g. what this study means to clinicians and policymakers
• Unanswered questions and recommendations for future research

Conclusions
This may be the only section readers look at, therefore write it carefully. Include primary conclusions and their implications, suggesting areas for further research if appropriate. Do not go beyond the data in the article.

Illustrations/photos/scans
• If illustrations submitted have been published elsewhere, the author(s) should provide consent to republication obtained from the copyright holder.
• Figures must be numbered in Arabic numerals and referred to in the text e.g. ‘(Fig. 1)’.
• Each figure must have a caption/legend: Fig. 1. Description (any abbreviations in full).
• All images must be of high enough resolution/quality for print.
• All illustrations (graphs, diagrams, charts, etc.) must be in PDF form.
• Ensure all graph axes are labelled appropriately, with a heading/description and units (as necessary) indicated. Do not include decimal places if not necessary e.g. 0; 1.0; 2.0; 3.0; 4.0 etc.
• Scans/photos showing a specific feature e.g. Intermediate magnification micrograph of a low malignant potential (LMP) mucinous ovarian tumour. (H&E stain). –include an arrow to show the tumour.
• Each image must be attached individually as a 'supplementary file' upon submission (not solely embedded in the accompanying manuscript) and named Fig. 1, Fig. 2, etc.

**Tables**
• Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged.
• Large tables will generally not be accepted for publication in their entirety. Please consider shortening and using the text to highlight specific important sections, or offer a large table as an addendum to the publication, but available in full on request from the author
• Embed/include each table in the manuscript Word file - do not provide separately as supplementary files.
• Number each table in Arabic numerals (Table 1, Table 2, etc.) and refer to consecutively in the text.
• Tables must be cell-based (i.e. not constructed with text boxes or tabs) and editable.
• Ensure each table has a concise title and column headings, and include units where necessary.
• Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

**Do not:** Use [Enter] within a row to make ‘new rows’:

**Rather:**
Each row of data must have its own proper row:

**Do not:** use separate columns for n and %:

**Rather:**
Combine into one column, n (%):

**Do not:** have overlapping categories, e.g.:

**Rather:**
Use <> symbols or numbers that don’t overlap:

**References**

**NB:** Only complete, correctly formatted reference lists in Vancouver style will be accepted. Reference lists must be generated manually and not with the use of reference manager software. Endnotes must not be used.

• Authors must verify references from original sources.
• Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6]
• All references should be listed at the end of the article in numerical order of appearance in the Vancouver style (not alphabetical order).
• Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus.
• Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al.
• Volume and issue numbers should be given.
• First and last page, in full, should be given e.g.: 1215-1217 not 1215-17.
• Wherever possible, references must be accompanied by a digital object identifier (DOI link). Authors are encouraged to use the DOI lookup service offered by CrossRef:
  ◦ On the Crossref homepage, paste the article title into the ‘Metadata search’ box.
  ◦ Look for the correct, matching article in the list of results.
  ◦ Click Actions > Cite
  ◦ Alongside 'url =' copy the URL between { }.
  ◦ Provide as follows, e.g.: https://doi.org/10.7196/07294.937.98x

Some examples:
• Legal references