# OUTCOMES FOLLOWING INTRAVITREAL BEVACIZUMAB FOR AGGRESSIVE POSTERIORLY LOCATED RETINOPATHY OF PREMATURITY AT A TERTIARY INSTITUTION

By

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Submitted in partial fulfilment of the academic requirements for the degree of MMed

In the department of Ophthalmology

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As the candidate's supervisor, I have approved this thesis for submission.

Signed:  Name: Dr Linda Visser Date: 8th June 2016

# Declaration

I DR TJ JORDAAN declare that:

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## Acknowledgements

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## Glossary of abbreviated terms

AP-ROP, aggressive posterior retinopathy of prematurity

APLROP, aggressive posteriorly located retinopathy of prematurity

BEAT-ROP, bevacizumab eliminates the angiogenic threat in ROP

CGA, corrected gestational age

CLT, conventional laser treatment

ET-ROP, early treatment of ROP

FDA, Food and drug administration

GA, gestational age

ICROP, The international classification of retinopathy of prematurity

ICU, intensive care unit

IVB, intravitreal bevacizumab

PPV, pars plana vitrectomy

RD, retinal detachment

ROP, retinopathy of prematurity

SD, standard deviation.

VEGF, vascular endothelial growth factor

## Overview of the thesis

Retinopathy of prematurity (ROP) is characterised by abnormal retinal angiogenesis occurring in premature and low birth weight neonates. In severe cases, it leads to proliferative retinopathy, vitreous haemorrhage, retinal detachment and subsequently blindness. ROP is one of the most common causes of preventable blindness. According to vision 20/20 ROP is the cause of 11% of childhood blindness in South Africa.

In patients with ROP, blindness or poor vision is most often ascribed to one of the following three entities:

- Threshold disease.
- Aggressive posterior retinopathy of prematurity (AP-ROP).
- Stage 3 disease in zone 1 with plus disease.

In this study, these entities are collectively referred to as "aggressive posteriorly located retinopathy of prematurity."

Historically patients who were classified with threshold disease were treated with either cryotherapy or conventional laser treatment (CLT). Currently the standard of care is to treat ROP patients with prethreshold type I disease with CLT. With this approach poor outcomes are reduced from 50% to 25%. Though this is an improvement the success rate is still poor.

In search of more effective means to treat ROP, alternatives have been explored. Bevacizumab, an anti-vascular endothelial growth factor that is Food and Drug Administration (FDA) approved for the treatment of colorectal cancer, has been used off-label intravitreally in ROP cases. In the Bevacizumab Eliminates the Angiogenic Threat in ROP (BEAT-ROP) trial patients had better outcomes when used for stage 3 disease in

zone I with plus, when compared to CLT. A lack of further randomized controlled trials on this issue, however, means that we still lack guidelines and treatment protocols to direct ROP treatment.

This study is a retrospective chart review to assess the outcomes of patients with aggressive posteriorly located ROP who were injected with intravitreal bevacizumab (IVB) at Inkosi Albert Luthuli Central Hospital between 2009 and 2016. Patient records on the hospital data base were analysed. The outcomes were assessed by analysing the gestational age, birth weight, corrected gestational age at time of intervention, other concurrent or subsequent interventional modalities as well as post intervention progression, regression or recurrence of the disease. Findings at discharge, including time to complete vascularisation and complications were also assessed. The defaulters were assessed separately.

Of the 33 patients, 64 eyes received IVB for aggressive posteriorly located ROP, of which 10 patients (20 eyes) defaulted follow up. Therefore 44 eyes of 23 patients were included in the main analysis. Of these patients 16 eyes also had CLT and seven eyes had pars plana vitrectomies. Intravitreal bevacizumab was administered at a mean of 35.27 weeks postmenstrual age. Regression and full vascularisation was documented in 36 eyes (81.8%) while 8 eyes (18.2%) progressed to retinal detachment. Seven of these eyes had a pars plana vitrectomy of which all, but one, had subsequent flat retinae at discharge. Thus, only one eye (2.27%) had a permanent inoperable retinal detachment. The eyes that progressed to retinal detachment received IVB at a mean of 1.31 weeks later than the eyes that regressed and vascularised fully. Of the 20 eyes of the patients who defaulted, five eyes (25%) had a permanent or inoperable retinal detachment at late follow up.

The important findings in our study were firstly that there seems to be a very specific time frame in which IVB works effectively and in this study sample there was a trend

towards progression to retinal detachment when this window period was missed. Secondly, there was a very high default rate with poorer outcomes seen in patients who defaulted treatment or follow-up. Most of the patients who followed up regularly had a favourable structural outcome. It is therefore essential to counsel the parents of ROP patients and to have measures in place to assure regular follow up.

In order to manage ROP effectively a multi modal approach is essential. Long term safety of IVB still needs to be established by future studies and therefore the potential risks and benefits must be weighed up carefully before IVB is considered for treatment of all ROP.

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# Part 1: The Review of Literature

## Introduction

Retinopathy of prematurity (ROP) is one of the most common causes of preventable blindness in preterm neonates.(1) South Africa is a middle income country with a declining infant mortality rate (32/1000 in 2016).(2) Thus, more infants, and among these an increasing number of low birth weight and less mature neonates, survive due to better neonatal care. Because these neonates have a higher risk of developing ROP, South Africa forms part of the so-called "third epidemic in ROP" (3). Despite the extent of this problem, there are still limited guidelines and protocols to direct the management of especially the most severe cases of ROP. With current standard of care treatment modalities, such as CLT, outcomes remain poor. Alternative treatment modalities have been implemented, however, with limited research regarding their efficacy and safety. More studies are needed to evaluate outcomes, guide future management, and safeguard medical practitioners against a rising threat of medical malpractice litigation.

## Pathogenesis of retinopathy of prematurity

ROP is caused by abnormal retinal angiogenesis in preterm and low birth weight neonates. It firstly comprises a delay in retinal vascular development and later also vasoproliferation which can lead to retinal detachment.(4) The first phase (22-30 weeks postmenstrual age) is characterised by relative hyperoxia and decreased vascular endothelial growth factor (VEGF) levels. The second phase (31-44 weeks postmenstrual age), by relative hypoxia and increased VEGF levels.(5)

Retinal angiogenesis starts at 4 months gestation and is only complete at 40 weeks gestation.(5) Exposure of the incompletely vascularised retina to high oxygen concentrations during periods of poor oxygen control, leads to down regulation of VEGF production and suppression of vessel migration.(6) Subsequently, as the eye grows the metabolic demand of the eye increases due to the state of relative hypoxia and thus there is an excessive release of VEGF which causes abnormal vasculogenesis. Blindness due to ROP is preventable if supplemental oxygen therapy is used appropriately and a screening programme is in place.(7)

## Screening protocol for retinopathy of prematurity

A proper screening program is essential in order to identify the patients at risk of developing ROP, but also to timeously diagnose the patients needing treatment. Guidelines developed by the ROP Working Group of South Africa in 2014 suggested the following criteria be used for ROP screening:

- Gestational age (GA) at birth of less than 32 weeks.(7)
- Birth weight of less than 1500 gram.(7)
- Preterm neonates weighing 1500-2000 gram, with additional risk factors including cardiac arrest, family history of ROP, hypoxic ischaemic encephalopathy, multiple blood transfusions, exchange transfusion or suboptimal oxygen monitoring.(7)

The Working Group also advocated for oxygen saturation levels to be kept between 88 - 92% in neonates receiving supplemental oxygen as a primary prevention measure.(7)

Screening can be stopped once the retina is fully vascularised or vascularisation into zone III (if no prior zone I or II ROP) or post menstrual age of 45 weeks (if no pre-threshold or

worse disease) or if regression of ROP took place (if no abnormal vascular tissue capable of activation or progression is present).(7)

## Classification of retinopathy of prematurity

The following criteria are the revised criteria according to the International Classification of Retinopathy of Prematurity, as formulated by an international consensus group of ophthalmologists(8)

The classification of ROP according to international standards involves types, zones, stages and extent of the disease. ROP can be broadly categorized into standard ROP and AP-ROP. ROP is additionally sub- classified in terms of the zones in which it occurs.

### Standard retinopathy of prematurity

The location of disease involvement in zones includes three possible zones

- Zone I: The innermost circle of which the radius extends from the middle of the optic disc to twice the distance between the centre of the disc and the centre of the macula.
- Zone II: An area extending centrifugally from the edge of zone I to the nasal ora serrata.
- Zone III: The residual temporal crescent anterior to zone II.

Furthermore, the severity of the disease is also classified according to the following stages:

- Stage 1: Presence of a thin line of demarcation between the vascularised and avascular retina.

- Stage 2: A ridge of demarcation that rises above the retinal surface.
- Stage 3: Extra-retinal fibrovascular proliferation or neovascularisation extending from the ridge into the vitreous. This stage can be further subdivided into mild, moderate and severe.
- Stage 4A: Partial retinal detachment not involving the fovea.
- Stage 4B: Partial retinal detachment with the fovea involved.
- Stage 5: Total retinal detachment

The extent of disease is described in clock hours or 30-degree sectors. The term "Plus disease" indicates a tendency of the disease to progress and is characterised by the presence of posterior pole venous dilatation and arterial tortuosity in at least 2 quadrants and if it becomes more severe, may include iris new vessels, poor pupillary dilatation and vitreous haze. Pre-plus disease is characterised by abnormal dilatation and tortuosity of the posterior pole vessels that are insufficient to be diagnosed as plus disease.

This schema was added based on findings from the ET-ROP study to help to determine whether to treat or to observe patients with ROP.(9)

Type 1: Higher risk patients that need laser photocoagulation within 72 hours

- Zone I any stage with plus
- Zone I, stage 3 without plus
- Zone II, stage 2/3 with plus

Type 2: Lower risk patients that should be observed twice a week

- Zone I, Stage 1/2 without plus
- Zone II Stage 3 without plus

In order to direct appropriate further treatment, and follow up intervals, it is very important to classify the patients correctly according to this classification. It is very important to be vigilant in diagnosing AP-ROP, which if missed, will have serious implications.

## Aggressive posterior retinopathy of prematurity

Aggressive posterior retinopathy of prematurity (AP-ROP) has also been referred to as "Type II ROP" or "Rush disease" and is an uncommon but very severe form of ROP.(8) If not treated appropriately and timeously it usually progresses rapidly to stage 5 ROP.(8) The characteristics of this type of ROP are the prominence of plus (in all 4 quadrants), posterior location (zone I or posterior zone II) and poorly-defined nature.(8) Other features include difficulty to distinguish between arterioles and venules due to shunting and it usually does not progress through the classical stages.(8) The junction of vascularised and avascular retina may appear featureless, with only a flat network of neovascularisation and often haemorrhages.(8) Less experienced practitioners can therefore easily miss AP-ROP.(8)

## Treatment of retinopathy of prematurity

ROP can be treated in various ways, including, but not limited to cryotherapy, conventional laser therapy (CLT), vitrectomy, and anti-vascular endothelial growth factor. These are briefly reviewed next.

### Cryotherapy

The multicentre CRYO for ROP (CRYO-ROP) trial showed a decrease in unfavourable outcomes and better visual function, when patients with bilateral threshold disease (i.e. 5 or more clock hours of stage 3 with plus ), were assigned to receive cryotherapy in one eye and no therapy for the fellow eye (control).(3) Almost half of the treated eyes had visual acuity of worse than 20/200 at 15 years of age.(3) Currently, cryotherapy is in general replaced by laser, but it is rarely still used in cases with a poor view of the retina, and cases with no equipment or expertise to perform indirect laser.(10)

### Conventional laser therapy

The Early Treatment of ROP (ET-ROP) trial showed significant improved outcomes with early laser treatment of type 1 (High risk), but not with type 2 (Low risk) prethreshold patients.(4) Current guidelines therefore recommend laser ablation of the avascular retina in type 1 and twice weekly observation of type 2 prethreshold ROP patients.(4) By treating the patients earlier, the unfavourable outcomes were decreased by 5% when compared to the treatment of threshold disease.(4)

If type 1 ROP is diagnosed, laser should be initiated within 72 hours.(4) Laser burns should be grey to grey-white and spaced one-half burn apart from ora serrata up to the ridge.(4) Care must be taken to assure complete treatment but also not to give too

aggressive burns.(4) To give laser treatment successfully is a skill that requires training and experience.(11)

CLT has a more predictable outcome and follow up period than IVB, due to many large prospective studies that have been published. Follow up time is also relatively shorter and there is no unknown potential systemic safety concerns, as there are with anti-VEGF.(12)

Disadvantages of CLT include systemic risks due to prolonged anaesthesia and apnoea, bradycardia and cardiopulmonary arrest.(13) Ocular complications include misplaced laser, vitreous haemorrhage, cataract, glaucoma, cystoid macular oedema, anterior segment ischaemia, macular dragging, myopia and phthisis bulbi.(13)

CLT for standard ROP is usually successful. However progression to retinal detachment occurs commonly with AP-ROP.(13) Several authors have reported poor outcomes when CLT was administered for AP-ROP, with the prevalence of retinal detachment ranging from 13-100%.(13) Other problems with laser for AP-ROP, because of persistent tunica vasculosa lentis, is a hazy view and difficulty to identify the border between vascularised and non-vascularised retina.(13) Laser therapy can also cause severe restriction in visual field due to an extensive area of retina that is ablated when it is required for very posterior disease.(13) A study done by Sanghi et al reported several risk factors for progression to retinal detachment after CLT including; GA under 29.5 weeks, haemorrhages, a need for repeat laser, new onset fibrovascular traction after laser, extensive fibrovascular proliferation (more than three clock hours of stage 3) and posterior zone I disease.(14) Therefore, although CLT is still the current standard of care modality for most cases of ROP, it is still far from the "gold standard", especially for the more aggressive and posteriorly located cases of ROP.

## Vitrectomy

Lens sparing vitrectomy is indicated when ROP progresses to stage 4A, 4B or stage 5. Scleral buckling for Stage 4A is also a treatment option but according to studies, causes macular anisometropia and has a much poorer macular reattachment rate (73% after vitrectomy compared to 31% after scleral buckling) and therefore should be avoided.(10) There are studies that showed good outcomes with early vitrectomy and lensectomy for AP-ROP cases that progressed to retinal detachment despite CLT.(15) Vitrectomy is therefore a vital "rescue" modality, especially in cases that responded poorly or progressed to retinal detachment, despite treatment with other modalities like CLT or IVB.

## Anti-vascular endothelial growth factor

Vascular endothelial growth factor (VEGF) plays a very important role in angiogenesis in several organs but especially the eyes, lungs and brain.(13) It also plays an important role in neuroprotection.(13) Although VEGF is very important for normal development, it is also a culprit in the pathogenesis of several diseases. These include diabetic macular oedema, neovascular age-related macular degeneration, metastatic tumours and ROP.

Bevacizumab is one of the anti-VEGF drugs and was approved by the FDA for chemotherapy of metastatic colon cancer in 2004.(16) Intravitreal bevacizumab (IVB) is however commonly used off-label as treatment for various forms of intraocular neovascularization, including use in ROP as monotherapy, but also in combination with CLT or vitrectomy.(5)

Bevacizumab is a 149 KDa, full-length, recombinant humanised monoclonal antibody that acts against VEGF-A by binding to its receptors on the surface of endothelial cells.(16) Ranibizumab and aflibercept are alternative anti-VEGF drugs that were specifically developed and approved by the FDA for use in neovascular age-related macular

degeneration.(16) The half-life of bevacizumab after intravitreal use in non-vitrectomised eyes is 9.82 days, compared to 7.15 days for ranibizumab.(17) Bevacizumab is cheaper than the other available anti-VEGF drugs and is therefore more accessible in resource limited settings. Bevacizumab was initially thought to be safer than the other available anti-VEGF drugs, because it is a larger molecule and considered less likely to cross the blood retinal barrier into the systemic circulation. It was, however, found that after IVB had been administered, serum levels of VEGF were lowered for a period of at least 7 weeks.(17) Ranibizumab on the other hand, lowered VEGF levels in the serum for 2 weeks, but it returned to normal 4 weeks post injection.(17) This raises the concern that ranibizumab may possibly be a safer alternative to bevacizumab.(17) Few small studies have shown good outcomes with intravitreal ranibizumab, but in some of the studies the recurrence rate was higher when compared to IVB.(18) Particularly in the preterm neonate, where vital organs are still developing, it may be a safer option to use ranibizumab. Evidence from large prospective studies is however still lacking.(17)

Before administering IVB it is very important to counsel the parents properly and to obtain informed consent.(11) IVB can be administered at the bedside or in theatre. It is very important to use a sterile technique to prevent endophthalmitis.(13) Bevacizumab 0.025ml (0.625mg) is administered at 1.5mm posterior to the limbus via a 32-gauge needle.(19)

Though certain disadvantages and risks are applicable with IVB treatment of ROP, certain positive outcomes and advantages are also evident. IVB can cause contraction of fibrovascular membranes when used in stage 4/5 ROP with resultant worsening of outcome.(20) Due to safety considerations IVB should not be used in ROP anterior to posterior zone II.(21) Another disadvantage of bevacizumab, is that it is effective only when administered in a certain window period. If administered before this time, there might be safety concerns, and after this time, the risk of progression to retinal detachment

is higher.(11) After IVB, vascularization is significantly delayed and therefore long-term follow-up is required, which can be burdensome, especially in resource limited settings.(12) Recurrences and progression of ROP do occur in a small but significant number of patients. There is also a risk of endophthalmitis or lens damage with IVB.(12) There are no long-term studies to prove adverse systemic effects, but some studies did show decreased levels of serum VEGF for up to 7 weeks after IVB.(17) This raises questions regarding safety, especially concerning neurologic and respiratory development.(21)

IVB has been shown to have a good outcome in cases with stage 3 ROP with plus in zone I.(5) The Bevacizumab Eliminates the Angiogenic Threat in ROP (BEAT-ROP) trial, showed significantly improved outcomes after first-line IVB (6% of patients had recurrences), when compared with laser (42% of patients had recurrences) for these patients.(5) AP-ROP in zone I, which usually has a very poor outcome with CLT, also showed good outcomes after first-line IVB.(13) IVB has also been used successfully as salvage therapy for threshold disease and progressing ROP after laser(19), and in cases where a vitreous haemorrhage or poor pupillary dilatation obscures the view to perform other interventions.(20) Cases have been described where IVB has been used as monotherapy or in combination with vitrectomy or laser, for severe ROP.(5) IVB acts more quickly than CLT. Advantages of IVB are also that it is a relatively cheaper option when compared to laser and is quick and easy to administer in either theatre or ICU.(5) In a condition where the time window to stop the neovascular drive is often very small, quick administration can make the difference between a good and a poor outcome.(7) In contrast to CLT the retina still continues to vascularise after IVB.(5)

It is advisable to refrain from administering IVB prophylactically for ROP, because of safety concerns. There are still many unanswered questions such as what is the ideal dosage, best time and indication for administration? The possible benefits of IVB

treatment for ROP are not well studied, though the BEAT-ROP study provides a good benchmark for further studies. The outcomes are briefly summarised below.

In the BEAT-ROP study the recurrence rate after IVB for zone I and posterior zone II disease combined was 6%, compared to 26% in the laser group. The difference in rate of recurrence between the two modalities was much bigger (42% for CLT and 6% for IVB) when zone I was assessed alone. Thus the difference in the recurrence rate between IVB and CLT for zone I was statistically significant, but not for zone II.(5) The mean period for recurrence was 16±4.6 weeks in the IVB group, compared to 6.2±5.7 weeks in the CLT group. (5)

Macular dragging was documented in 1.4% of eyes in the IVB group compared to 30.1% in the CLT group.(5) Vascularisation continued in the IVB group whereas it halted in the CLT group.(5) The rate of progression of ROP and defaulting was not indicated. Seven deaths occurred of which five were in the IVB group.(5) This difference is important, even though it is not a statistically significant difference, especially since 4 of the 5 cases were due to pulmonary causes.(19)

## Defaulting

High default rates occur in several ROP studies. In a large prospective study performed at a tertiary hospital (Chris Hani Baragwanath Hospital, Soweto), 48.8% of the 84 patients diagnosed with ROP defaulted follow up.(1) Possible reasons for this poor follow up rate could be linked to poverty, poor social support structures, transport, and the physical and psychological burden of having a preterm baby in ICU for a prolonged period of time.

## Medico-legal considerations

There is a big shift in focus from the road accident fund towards medical malpractice claims among lawyers, since recent changes to the road accident fund made it more difficult for lawyers to succeed in claims.(23) The number of medical malpractice claims in excess of 5 million rand increased by 900% over the past decade. ROP cases, specifically in the public sector, have become sought-after among some lawyers because they know how difficult these cases are to defend and how easy it is to prove that at some point in time, medical mismanagement occurred.(23) Resource limitations in the public sector leave a lot of room for mismanagement to occur somewhere in the multi-disciplinary chain. It is therefore of cardinal importance to conduct further research in this field to develop treatment modalities and guidelines that are evidence-based.

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# Part 2: A submission ready manuscript

## Cover Page

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## Summary

Number of words: Abstract: 247; Article: Introduction: 637; Research methods and design: 412; Results: 660; Discussion: 1649; Conclusion: 151; Total: 3850

Pages: 19; Tables: 0; Figures: 4

# OUTCOMES FOLLOWING INTRAVITREAL BEVACIZUMAB FOR AGGRESSIVE POSTERIORLY LOCATED RETINOPATHY OF PREMATURITY AT A TERTIARY INSTITUTION

**Background** Retinopathy of prematurity is an important cause of childhood blindness and conventional treatment modalities lead to significant visual morbidity. Alternative treatment modalities need to be explored.

**Aim** To analyse outcomes following intravitreal bevacizumab (IVB) for the treatment of aggressive posteriorly located retinopathy of prematurity (ROP) at a tertiary institution.

**Setting** Inkosi Albert Luthuli Central Hospital, a tertiary hospital in Durban, draining patients across KwaZulu-Natal.

**Methods** A retrospective chart review of patients treated between January 2009 and December 2016. Outcomes were assessed by analysing the gestational age, birth weight, gestational age at time of intervention, stage and zone of ROP, other concurrent or subsequent interventional modalities, as well as progression, regression or recurrence of the disease post intervention and complications. Thirty-three patients (64 eyes) received IVB, of whom ten patients (20 eyes) defaulted follow up, leaving 23 patients (44 eyes) to qualify for the study.

**Results** Of the 44 eyes, 36 (81.8%) regressed and vascularised fully or up to the lasered retina, 8 (18.2%) progressed to retinal detachment, of which 7 were surgically reattached and one (2.3%) remained permanently detached. Of the 20 eyes from the 10 defaulters, 5 (25%) had inoperable retinal detachments.

**Conclusion** The majority of patients, who complied with ROP treatment and were followed up regularly, had a favourable structural outcome when IVB was used concurrently with other treatment modalities. There was a trend towards progression to

retinal detachment in eyes where IVB was administered relatively later during the course of the disease process.

## Introduction

Retinopathy of prematurity (ROP) is one of the most common causes of visual morbidity and preventable childhood blindness in the world.(1) South Africa is a middle income country with a declining infant mortality rate of 32/1000 in 2016.(2) Thus, more infants, and among these an increasing number of low birth weight and less mature neonates, survive due to better neonatal care. Due to these neonates having a higher risk of developing ROP, South Africa forms part of the so-called "third epidemic in ROP".(3) ROP also results in a large number of large medico-legal cases against medical professionals. Despite the serious nature and implications of this disease, there is a lack of evidence-based guidelines regarding intravitreal bevacizumab (IVB) treatment for ROP. A review of outcomes following IVB and subsequent update of the guidelines may promote a better outcome for these patients.

The current standard treatment of ROP, according to the Early Treatment of Retinopathy of Prematurity (ET-ROP) study, is conventional laser therapy (CLT) to the peripheral avascular retina for prethreshold type I disease, and twice weekly observation of type II prethreshold ROP.(4)(5) By treating the patients earlier, the unfavourable outcomes were decreased by 5% when compared to the treatment of threshold disease.(4) CLT has a predictable outcome, requires a short follow up period and there are no unknown potential systemic safety concerns, but there are also major disadvantages.(5) Disadvantages of CLT include systemic risks due to prolonged anaesthesia, apnoea, bradycardia and cardiopulmonary arrest.(6) Ocular complications include misplaced laser, vitreous haemorrhage, cataract, anterior segment ischaemia, glaucoma, cystoid macular oedema, macular dragging, myopia, restricted visual field and phthisis bulbi.(6)

CLT for standard ROP is usually successful, however progression to retinal detachment occurs commonly with Aggressive Posterior ROP (AP-ROP), with the prevalence of retinal detachment ranging from 13-100%.(6) Thus the problem with laser treatment is that it requires a high level of experience and expensive equipment to perform effectively and often leads to significant visual morbidity.(6) Therefore, although CLT is still regarded as the standard of care for most cases of ROP, it is far from the "gold standard", especially for the more posteriorly located cases of ROP.

In a search for alternative treatment modalities, the Bevacizumab Eliminates the Angiogenic Threat in Retinopathy of Prematurity (BEAT-ROP) trial, showed that patients with stage 3 disease in zone I with plus, had better outcomes when treated with intravitreal bevacizumab compared to treatment with CLT.(7)

Spandau et al reported good outcomes after first-line IVB for AP-ROP in zone I.(6) IVB has also been used successfully as monotherapy or in combination with other modalities for salvage therapy for threshold disease, progressing ROP after laser and in cases where a vitreous haemorrhage or poor pupillary dilatation obscures the view to perform CLT.(8,9) Although some clinicians report improved outcomes with IVB treatment, only a few studies have been done to describe the outcomes of these patients.(6-9)

Patients included in the present study received IVB for stage 3 disease with plus in zone I, for aggressive posterior ROP (AP-ROP) and for posterior threshold disease. For the purposes of this study these three indications for IVB are collectively referred to as aggressive posteriorly located retinopathy of prematurity (henceforth abbreviated APLROP).

This study, directed to add to the evidence-base of IVB treatment, is a retrospective chart review to determine the outcomes of premature and low birth weight infants who presented with APLROP, and were treated with IVB, between 2009 and 2016 at Inkosi

Albert Luthuli Central Hospital (IALCH). The outcomes were assessed according to post-interventional progression, recurrence, regression, full vascularisation and complications that occurred during the follow up. The defaulters were analysed separately.

Some of the outcomes have not been described in the literature before and results of this study can therefore contribute to improved future treatment protocols and help to alleviate the burden of visual morbidity caused by ROP.

## Research method and design

### Study design

A retrospective descriptive chart review was done by analysing the clinical documents entered for these patients on the computer database (Soarian system) at IALCH between January 2009 and December 2016. The demographical information was recorded including race, gender, birth weight and gestational age (GA). The corrected gestational age (CGA) at the time of intervention and subsequent full vascularisation, as well as the period in weeks between injection and full vascularisation, were documented. The response to IVB was assessed by analysing the patient's clinical documents for progression, recurrence, regression and further vascularisation. The structural outcomes were analysed, looking at progression to retinal detachment, full vascularisation and complications such as myopia, macular dragging and permanent or inoperable retinal detachment. Patients who defaulted treatment or follow up, were excluded from the main analysis, but were analysed separately.

### Setting

IALCH is a tertiary hospital treating patients from across KwaZulu-Natal. The ophthalmology clinic at IALCH receives patients from several peripheral ophthalmology clinics. During the study period patients were screened according to the guidelines of

the ROP Working Group of South Africa.(10) Patients were diagnosed according to the International Classification of Retinopathy of Prematurity (ICROP).(11) Injections of 0.625 mg Bevacizumab were administered intravitreally, 1.5 mm from the limbus via sterile technique and under general anaesthesia in theatre. Patients were followed up until first documentation of full vascularisation with complete regression in both eyes, and then referred to the base hospitals.

## Data collection

Data was collected from the Soarian electronic data base at IALCH and analysed with Microsoft Excel. A password was used on the relevant computer to assure patient confidentiality.

## Data analyses

Data were analysed descriptively and means (±SD) were presented for continuous variables, and frequencies (%) were presented for categorical variables. All these analyses were done using Microsoft excel.

A Chi-squared test was used to determine whether there was a statistically significant difference in the number of documented permanent retinal detachments, between the patients who defaulted follow up, and those who complied with further follow up.

Non-parametric statistics were used to determine whether there was a statistically significant difference in the CGA at time of IVB administration, between the group that vascularised fully and the group that progressed to retinal detachment.

## Ethical considerations

The Provincial Health Research Committee (PHRC) and University of KwaZulu-Natal Biomedical Research and Ethics Committee (BREC, BE008/15), approval was obtained.

Site permission was obtained from Inkosi Albert Luthuli Central Hospital's medical manager. During this research, the Declaration of Helsinki was adhered to.

## Results

In this sample, the incidence of APLROP in infants diagnosed with ROP steadily declined, from a peak incidence of 12 infants in 2012 to two infants in 2016 (figure 1).

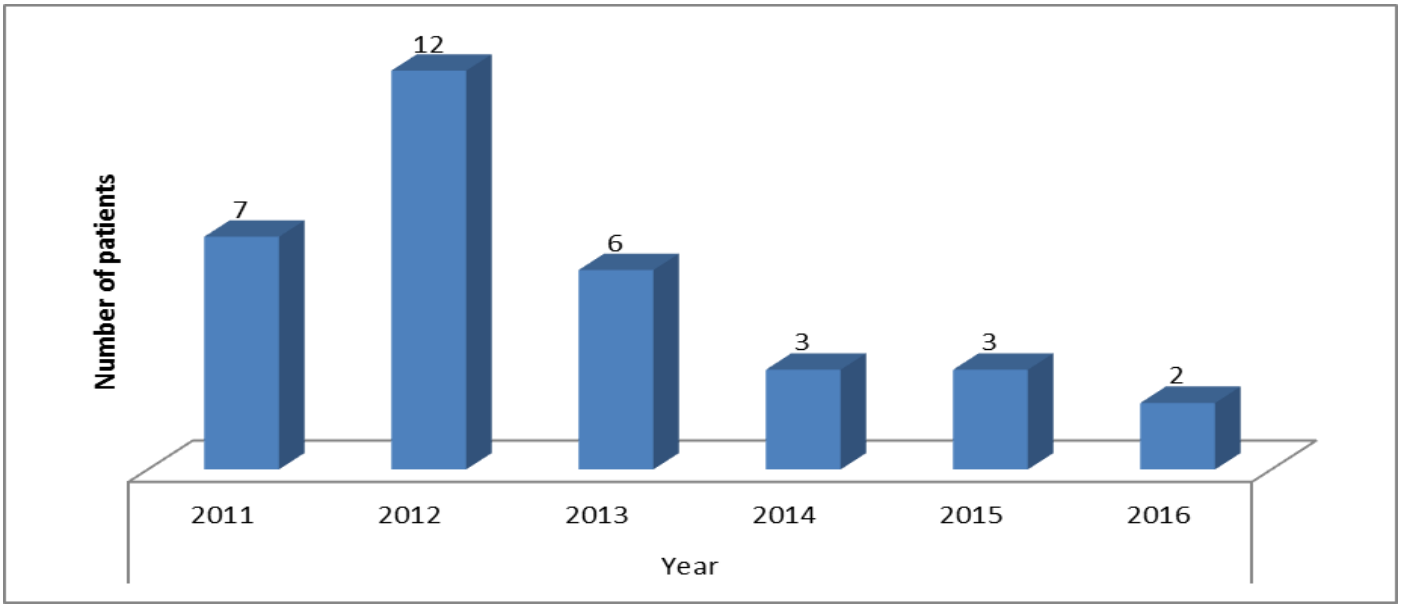


**Figure 1**: **Number of patients diagnosed with APLROP and injected with IVB during each year of the study period**

Sixty-four eyes of 33 patients with APLROP received IVB injections between January 2009 and December 2016. Ten patients (20 eyes) defaulted follow up to an extent that it significantly influenced their outcome. Thus 44 eyes of 23 patients qualified for the study. The mean GA was 28.4 ± 1.7 weeks and the mean weight was 0.99 ± 0.2 kg, at birth.

Of the 23 patients, 18 were black, three were Indian, one was of mixed race and one was white, largely mirroring the population demographics of the province.

The indication for IVB was AP-ROP in 38 eyes, posterior threshold disease in three eyes and stage 3 disease in zone I with plus in a further three eyes.

Seven eyes had a limited PPV after progression to stage 4A/B post IVB and 16 eyes had CLT. Three of the 16 eyes had CLT at three to four weeks post IVB due to early progression and the rest had CLT at the time of the IVB injection, because during this period, the efficacy of IVB was not established yet. Ten of the 16 eyes had CLT in 2011. Figure 2 indicates the number of the specific interventional modalities per year of the study period.

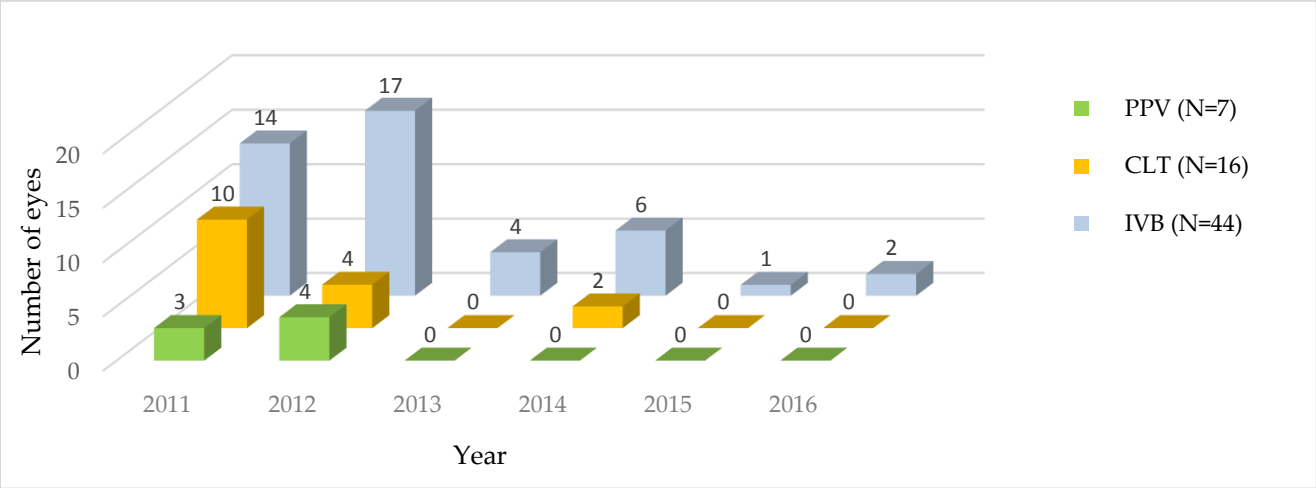


**Figure 2: Number of specific interventional modalities per year**

Bevacizumab was injected at a mean CGA of 35.2 ± 2.3 weeks. The mean CGA at first documentation of full vascularisation was 52 ± 8.8 weeks, which increased to 55 ± 8.7 weeks when the lasered eyes were excluded. The period between injection and full vascularisation was a mean of 17.9 ± 9.5 weeks. Thirty-six eyes (81.8%) regressed and vascularised fully or up to the lasered retina.

The eyes that regressed and vascularised fully received IVB at a mean CGA of 34.9 weeks, while the eyes that progressed to retinal detachment received IVB at a mean CGA of 36.3 weeks, a mean of 1.31 weeks later than the eyes that regressed and vascularised fully. This difference was statistically significant (p=0.047), (Cohen's D = 0.5565)

Eight eyes progressed to retinal detachment. Of these, six eyes progressed to stage 4A, one eye to stage 4B and one eye to stage 5 disease. The parents of one of the patients that progressed to stage 4A refused surgery, thus seven eyes underwent vitrectomies with eventual flat retinae in six of these eyes. One eye, initially diagnosed with threshold disease described as 12 clock hours of stage 3 disease in zone I with plus and progressing to stage 5 after IVB, remained detached after surgery. At the time of his PPV it was documented that there were five retinal holes and a fold over the macula and a decision was made not to reoperate due to a poor prognosis for vision. The retinal detachment in the eye of the patient where surgery had been refused by the parents did not progress but instead the eye developed cicatricial ROP with a dragged, but flat retina at final examination. In total, therefore 43 eyes had documented flat retinae.

Myopia was documented in ten eyes, eight of which had high myopia. The majority (80%) of these received CLT. There were two eyes that had documented macular dragging (figure 3). Of the sixteen that had IVB and CLT, eight eyes (50%) had documented myopia, compared to two of 28 eyes (7.1%) only receiving IVB. No recurrence of ROP occurred and no patients were re-injected with bevacizumab. No deaths were documented.

The rate of complications or poor structural outcome steadily decreased after 2011 (figure 3).

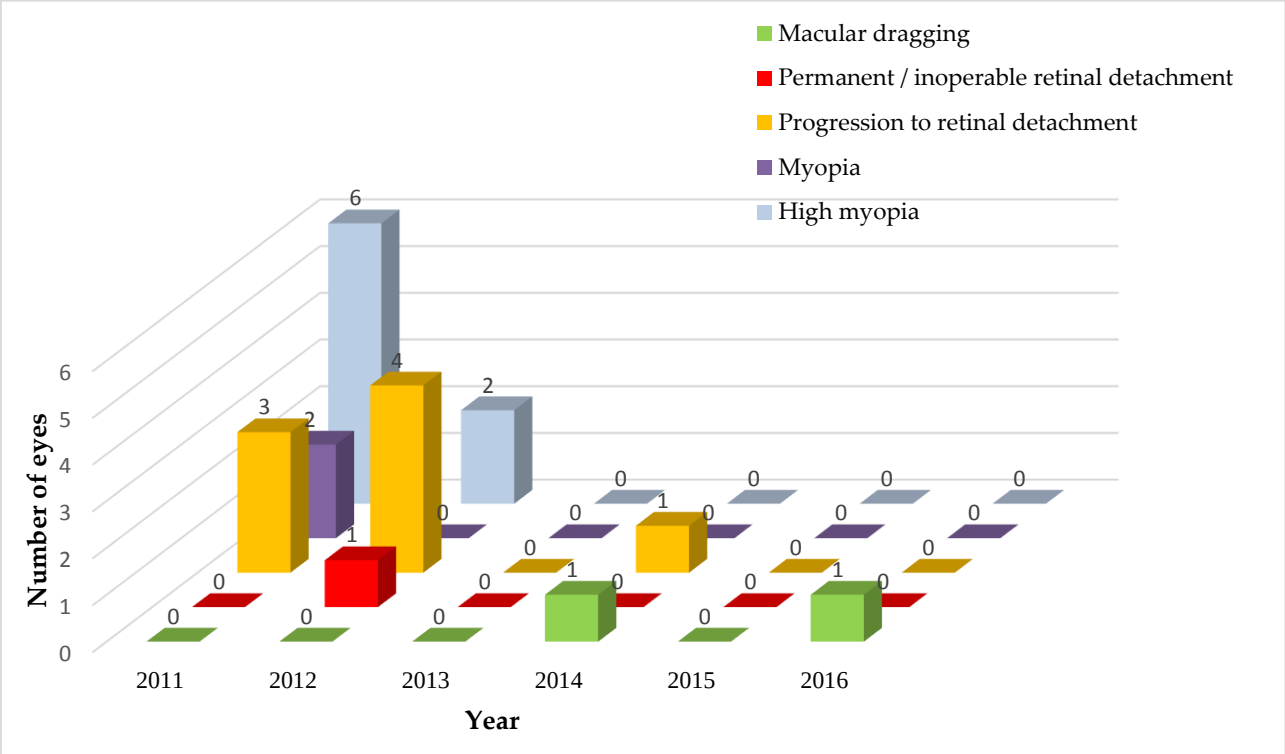


**Figure 3: Annual structural outcome**

Of the 20 eyes from the 10 patients who defaulted treatment, five eyes (25%) had documented retinal detachments ranging from stage 4B/stage 5 to cicatricial ROP. A Chi-squared test was used to determine whether there was a statistically significant difference in the number of documented permanent retinal detachments between the patients defaulting follow up (25%) and those complying with follow up (2.3%). This difference was statistically significant (Non-parametric analysis; asymptomatic significance 2-sided=0.004, $p<0.01$).

## The discussion

### Discussion of key findings

In this study of patients with APLROP, injected with IVB, a favourable structural outcome was seen in the majority of patients and important trends were observed which can aid to improve guidelines and management of our ROP patients.

The incidence of aggressive posteriorly located ROP decreased steadily since a peak in 2012. The likely explanation for the declining incidence is better neonatal care and better oxygen monitoring.

Of the eyes injected with IVB, 81.8% responded well to IVB and had documented full vascularisation after regression of the disease. Eight eyes (18.2%) responded poorly to treatment and progressed to retinal detachment. Most of the eyes that progressed to detachment also received CLT. Sanghi et al reported progression to retinal detachment in 17.4% of 109 eyes diagnosed with AP-ROP and treated with CLT.(12) Sanghi's sample however was only AP-ROP patients and they were treated with only CLT, it can however be concluded that the results in this study were at least as good. Of the 44 eyes in this study, 38 eyes had AP-ROP of which 6 eyes progressed to retinal detachment. Therefore 15.8% of the eyes diagnosed with AP-ROP, progressed to retinal detachment and all of these eyes were treated with both bevacizumab and CLT. None of the eyes with AP-ROP that were treated with only bevacizumab progressed. Out of the 16 eyes that were treated with CLT and bevacizumab 8 eyes progressed (50%) which is a significant high number of eyes that progressed among the CLT group. Among the 8 eyes that progressed 6 eyes received CLT for zone 1 disease which may be the reason for the poor outcome in this subgroup. This study sample however, was not large enough to make significant conclusions from subgroup comparisons.

In this study, there was early progression at a mean CGA of 38.9 weeks and thus a mean of 2.62 weeks after the IVB injection and in six of the eight eyes, progression shortly followed CLT. A more fulminant disease process, necessitating 'rescue' laser therapy is a possible explanation but it should be considered that the laser treatment could have contributed to the progression. It is described that incomplete or aggressive laser therapy can worsen the progression of ROP.(13) There is therefore a suspicion of inadequate or aggressive laser therapy in some of the patients in our study population.

In this study, there were no recurrences in contrast to the BEAT-ROP trial where there were late recurrences in the IVB group, at a mean of 16±4.6 weeks after IVB, compared to early recurrences at 6.2±5.7 weeks after CLT. (8). A possible explanation for our low recurrence rate could be the fact that, unlike the cohort in the BEAT-ROP trial (mean GA of 25.4 weeks), our babies were relatively more mature (mean GA of 28.4 weeks) and therefore vascularisation occurred before the effect of the bevacizumab had worn off.

Out of the 44 eyes that qualified for the study, the structural outcomes were favourable with only one eye with a permanent retinal detachment, ten eyes with myopia and two eyes with macular dragging. The rate of complications and poor structural outcomes decreased significantly after 2012 as illustrated in figure 3. The structural outcomes in patients who received IVB and CLT were poorer than the patients who received IVB only. A higher rate of myopia and progression to retinal detachment were documented in the combined CLT and IVB group. Myopia was documented in 50% of the eyes that had CLT and IVB, while it was only documented in 7.1% of the eyes that had only IVB. This trend was very similar to the outcomes of a follow up study done on the BEAT-ROP participants for zone I disease in which very high myopia was documented in 3.8% in the IVB group, compared to 51.4% in the CLT group.(14) Some of the patients were not

followed up long term and therefore refractions were not done on them. As a result, the incidence of myopia might be higher than what was documented.

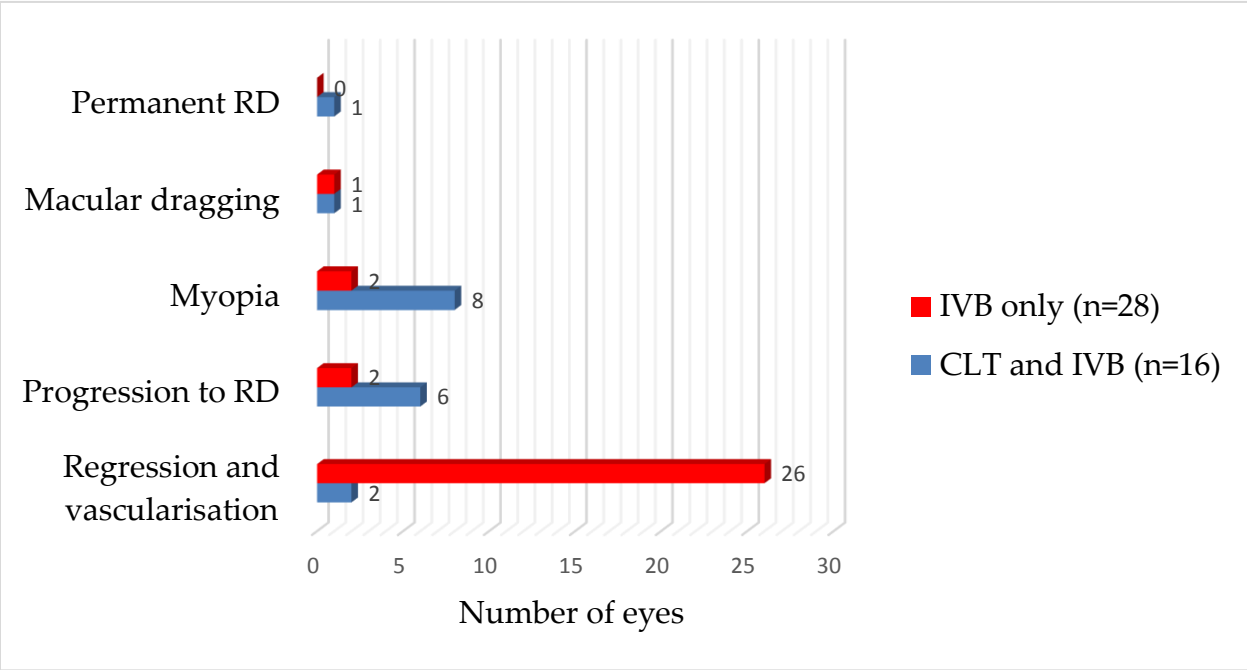


**Figure 4: Structural outcome comparing IVB and CLT with IVB only**

Vascularisation was delayed and full vascularisation was documented at a mean of 17.9 ± 9.5 weeks post IVB and a mean CGA of 55 weeks in eyes that did not receive laser. These findings correlated well with the findings from other studies that also showed delayed vascularisation after IVB.(7) This emphasizes the fact that patients who receive IVB need to be followed up for longer periods than patients who are treated with other modalities such as CLT.(4)

There was a significantly high default rate (30.3%) among the patients diagnosed with APLROP. This default rate was less than the 48.8% among patients diagnosed with ROP in a large prospective study done at Chris Hani Baragwanath Hospital between 2001 and 2003, but still high enough to raise concern.(1) There is a trend towards a high default

rate among ROP patients. Possible reasons for this poor follow up rate could be linked to poverty, poor social support structures and lack of transport. The physical and psychological burden of having a preterm baby in ICU for a prolonged period can also contribute to poor compliance with the management plan.

The percentage of eyes that progressed to permanent or inoperable retinal detachment was significantly higher among the patients that defaulted follow up compared to the patients that followed up regularly (25% compared to 2.75%). It is therefore very important to have systems in place to encourage regular follow up, but also to recruit defaulters. This high default rate and poor outcome among the defaulters have not been described in literature before.

There was a trend towards progression to retinal detachment in eyes that received IVB relatively later during the course of the disease process. This is also a very important finding that has not been described in literature before. The difference in the interval was found to be statistically significant. In a condition where the time window to stop the neovascular drive is often very small, timeous administration of IVB can make the difference between a good and a poor outcome.(10) The exact reason why time is such a critical aspect is not known, but it might be related to the contraction of fibrovascular membranes post IVB administration.(12) This trend can possibly be explained by the equilibrium between connective tissue growth factor and vascular endothelial growth factor, and the triggering of the angio-fibrotic switch by anti-VEGF as described by Kuiper and colleagues.(15)

CLT was administered less liberally after 2011 especially for zone I disease. 87.5% of the CLT in this study occurred in 2011 and 2012 (figure 2). Most of these eyes had zone I disease and documented high myopia at later follow up. After 2012 CLT was used much less often for zone I disease. This trend was most probably a natural response to the poor structural outcomes of these patients. The outcomes of these patients were very similar to the outcomes of a follow up trial that was done on the BEAT-ROP patients by Geloneck et al in which 51.4% of the patients in the CLT-group had documented very high myopia.(14)

## Strengths and limitations of this study

This was a retrospective study and posed the characteristic limitations associated with retrospective studies. Different modalities of treatment were used with three different indications for IVB, which caused difficulty in ascribing changes to a specific treatment modality. Patients were also assessed by multiple doctors with different levels of experience which compromised stability in the variables further. The disease entity studied is rare and therefore a relatively long study period is needed to acquire a meaningful population sample. The outcomes of treated patients were influenced by multiple risk factors and comorbidities, which were inconsistently documented in the clinical notes. The aim of this study was therefore to observe trends rather than make absolute conclusions regarding ROP treatment and outcomes.

## Recommendations for the ROP policy or guidelines

This study shed some light on a few aspects on which we can work in order to improve the quality of management of ROP patients.

The most important aspect is to inform, educate and counsel parents thoroughly regarding ROP in general and the importance of regular follow up, in order to establish

better compliance with the treatment and follow up plan. A plan should be in place to trace parents who default treatment, such as acquiring collateral contact information or liaising with the base hospital or paediatric unit to recruit these patients.

Detailed and complete clinical note keeping is essential in order to manage these patients better but also to monitor outcomes more accurately and to serve as a buffer in case of medico-legal litigation. More objective monitoring of ROP by means of fundus photography and fluorescein angiography will be of great benefit in ROP management and to audit the outcomes.

There should be better collaboration with the neonatal unit and paediatric department in order to improve oxygen monitoring, neonatal care and appropriate or timeous referral for screening. A formal protocol will help to standardise ROP management between all the relevant role players and to avoid unnecessary deviation and pitfalls.

CLT of very posterior disease especially zone I disease should be avoided.

Positive aspects of our ROP management are also highlighted and can be further expanded in order to improve the level of care of patients. These include an excellent screening facility, good infrastructure, good equipment and a fully functional retinal surgery service at the same facility.

## Suggestions for future research

Safety is still a concern and this study was not powered to evaluate safety aspects of IVB. Further studies are needed to investigate the ideal dosage and timing of, as well as indications for IVB. Studies are also needed to establish the role of ranibizumab in treatment of ROP. A prospective study on ROP will serve a vital role in helping to expand on the existing data base.

## Conclusion

Most patients in this study had a favourable structural outcome when they were followed up regularly, but very poor outcomes were seen among the patients who defaulted follow up. There were also a very high number of patients that defaulted follow up.

A longer follow up period is required for babies receiving IVB, as opposed to CLT. Also proper counselling and measures to ensure or encourage regular follow up may contribute toward a better outcome in patients diagnosed with ROP.(4)

From this study, it can be concluded that IVB is of great benefit in patients with APLROP, though other modalities such as CLT and PPV are still essential in managing some patients. Patients with very advanced disease at the first presentation tend to have a poorer outcome. Furthermore, because APLROP rapidly progresses, timeous intervention without delay is essential. Later treatment can trigger the angio-fibrotic switch which may lead to adverse outcomes.

## Acknowledgements

Dr Linda Visser - Head of Department Ophthalmology, UKZN

Prof. Sartorius - Department Public Health, UKZN

Aldine Oosthuyzen - Manager information Technology, NWU

Prof Colleen Aldous - Medical Research Scientist, UKZN

## Competing interests

The authors declare that they have no financial or personal relationship that may have inappropriately influenced them in writing this article.

## Authors' contributions

Dr T.J. Jordaan was the project leader. Dr T.J. Jordaan and Dr L. Visser were responsible for the project design. Statistical calculations were performed by Ms. Aldine Oosthuysen.

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# Appendix 1: The final Study Protocol

**PROTOCOL NUMBER:**


## BIOMEDICAL RESEARCH ETHICS COMMITTEE

## EXPEDITED APPLICATION FORM[1]

Application to the UKZN Research Ethics Committee for ethics review of new research projects

*(For research on human participants)*

**RESEARCH OFFICE CONTACT DETAILS:** Biomedical Research Ethics Administration, Westville Campus, Govan Mbeki Building, Private Bag X 54001, Durban, 4000, KwaZulu-Natal, South Africa; Tel: +27 31 2602486; Fax: +27 31 2604609; Email: BREC@ukzn.ac.za ;

Website: http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx

| SECTION A: | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **APPLICANT/PRINCIPAL INVESTIGATOR:** *reporting purposes* | | | | | | | | | | * For UKZN statistical |
| Title: Mr | | Ms | | Mrs | | Dr | ✓ | Prof | | *(Select option)* |
| Name : Thomas Johannes Jordaan | | | | | | | | | | |
| *Gender: Male | | | | | | | | | | |
| *Race: Caucasian | | | | | | | | | | |
| UKZN College: Health Sciences | | | | | | | | | | |
| UKZN School/Discipline | Nelson R Mandela School of Medicine/ Ophthalmology | | | | | | | N A | | |

[1] Note: This application must be self-sufficient. Sections marked "see protocol" are unacceptable and will be returned to the applicant.

| | | | |
|---|---|---|---|
| Hospital/Institution where employed: | King Edward Hospital | N A | |

| | |
|---|---|
| Professional status: | Registrar in Ophthalmology |
| Postal address: | 113 Eleventh Avenue, Morningside,Durban,4001 |
| Contact phone Numbers:<br>Office: | |
| Mobile number: | 0834478029 |
| Fax number: | |
| Email address: | tommiejordaan@yahoo.com |
| Full/Part time Employment: | Full time |
| Current HPCSA Number (or equivalent): | MP0597694<br>*if registration is pending, submit proof of application |

| Purpose of research: If postgraduate degree<br>*(Please tick)* | Hons | MMedSc | MMed | MSc | MFamMed | MChB | PhD | N/A |
|---|---|---|---|---|---|---|---|---|
| | | | ✓ | | | | | |

| | |
|---|---|
| Other degree not listed above: | N/A |
| Student Number and year of study: (*if applicable)213574211 , Second year* | |

| | | | |
|---|---|---|---|
| If for postgraduate degree, please confirm whether the application has been reviewed and approved by your school's Academic Leader (Research): | Yes | | No ✓ |
| If yes, provide approval date and attach approval letter: | 23 December 2016 | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Name and qualifications of Supervisor Dr L Visser, MBChB, MMed(Ophth), FCS(SA)Ophth | | | | | | |
| Name and qualifications of Co-supervisor N/A | | | | | | |
| If not for degree purposes, state other (example, self-initiated research): | | | | | | |
| Has this study been, or is it likely to be, submitted to any other Research Ethics Committee? | Yes | | No | ✓ | N/A | |
| If yes, please name the Committee/s and or institution and give outcome - i.e. approved/rejected/pending/not applicable? *(If approved, attach approval letter)* | | | | | | |
| **Please state number of Co-investigators in project:[2]**<br>**(if additional space is required for more investigators details please add to the end of application)** | | | | | | |
| **CO-INVESTIGATOR/S ROLE IN PROJECT** ** For UKZN statistical reporting purposes* | | | | | | |
| Name: N/A | | | | | | |
| Faculty: | | | | | | |
| Department: | | | | | | |
| *Gender: | | | | | | |
| *Race: | | | | | | |
| Role: | | | | | | |

[2] Please note that because of conflict of roles and interests that can arise, academic supervisors and co-investigators should be separate individuals.

| |
|---|
| Signature of Co-Investigator: |
| Name: N/A |
| Faculty: |
| Department: |
| *Gender: |
| *Race: |
| Role: |
| Signature of Co-Investigator: |
| |
| Name: N/A |
| Faculty: |
| Department: |
| *Gender: |
| *Race: |
| Role: |
| Signature of Co-Investigator: |

| | | | | |
|---|---|---|---|---|
| Has the Principal Investigator or any of the co-investigators been previously/or are presently being investigated for alleged research misconduct?<br>*(If yes, please provide details and dates)* | Yes | | No | ✓ |
| **FUNDING OF THE RESEARCH:** | | | | |
| Has funding been secured? | Yes | | No | N/A |
| Amount: R | | | | |
| Name of funder: *(full details)* | | | | |
| Is this project funded from a US DHHS funding source? | Yes | | No | ✓ |
| If yes, name the federal funagency: | | | | |
| Can this project proceed without funding?<br>*(give a brief explanation)* | Yes | ✓ | No | |
| Has an application for funds been made to other sources to support this project? | Yes | | No | ✓ |
| If yes, state name/s of funding agency and amount requested: | | | | |
| **Note:**<br>For all US Federally funded studies (e.g. NIH, CDC, NIAID, DAIDS, NIMH, etc), one complete copy of the original funding application and approval must accompany the BREC ethics application. | | | | |

All University contracts need to be uploaded on the Contracts Management online submission form with either the signed **Approval letter** (non-research) **or Form 1**(research related). The website link to the system is http://legalservices.ukzn.ac.za/ContractsManagement.aspx

If you require assistance with the completion of the online submission form, or with any aspect of the new system, please contact Mr Rendra Phalad on Ext 7455 for all contracts (non-research contracts), and Mr Deon Moodley on Ext 8199 (for research contracts).

**FAILURE TO MAKE FULL FINANCIAL DISCLOSURES WILL DELAY ETHICS APPROVAL**

| | | | | |
|---|---|---|---|---|
| Please indicate whether a BREC review fee is applicable for this study?<br>(See Fee Schedule on BREC Website) | Yes | | No | ✓ |
| If Yes, is the study covered by your Centre/Unit's annual levy fee to BREC? | Yes | | No | |

**Note:**

* Expedited review only applies to minimal risk studies – e.g. retrospective chart reviews, studies on stored samples etc., for details see BREC ToR and SoP at

*http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx*

## SECTION B:

### NATURE OF STUDY

### Quantitative

| Type of Study: *(please tick)* | Epidemiological | Observational clinical study | Experimental | Observational | |
|---|---|---|---|---|---|
| | Retrospective Chart Review ✓ | Prospective Chart Review | Laboratory study on stored samples | Audit | Other:(Specify) |

### Qualitative

N/A

### 1. THE PROTOCOL FOR STUDY

1.1 **Full title of research project**: *(Please DO NOT use abbreviations or acronyms)*

Outcomes following intravitreal bevacizumab for aggressive posterior retinopathy of prematurity at a tertiary institution.

**1.2 Where will the Research be carried out? (Hospital, clinic etc.).**

Inkosi Albert Luthuli Central Hospital

800 Vusi Mzimela Road (Bellair Road)

Cato Manor

Durban

**1.3 Aims (what you hope to achieve) and objectives (how you will achieve your aims) of study:**
*(please list)*

Aim: To determine the outcome of patients treated with intravitreal bevacizumab for aggressive posterior retinopathy of prematurity at Albert Luthuli Hospital since 2011.

Objectives:

To determine the outcome of AP-ROP patients treated with IVB only.

To determine the outcome of AP-ROP patients treated with IVB and conventional laser treatment (CLT).

Outcome will be assessed by analysing the following data on each subject:

- Gestational age, date of birth, birth-weight
- Post conceptual gestational age at time of intervention
- Stage and zone of ROP at time of intervention
- Interventional modalities (IVB, CLT, Pars plana vitrectomy)
- Progression of the disease

- Recurrence of disease
- Regression of disease
- Extent of vascularization
- Complications
- Corrected gestational age (CGA) at discharge

**1.4 Hypothesis to be tested, or Research Question to be answered:**

Is intravitreal bevacizumab effective in the treatment of aggressive posterior retinopathy of prematurity?

**1.5 Summary of the proposed research (restrict to 100 words)**

A retrospective chart review of the outcome of patients diagnosed with aggressive posterior retinopathy of prematurity and treated with intravitreal bevacizumab at Inkosi Albert Luthuli Central Hospital since January 2011.

**1.6 Keywords (for database):**

Intravitreal bevacizumab, Aggressive posterior retinopathy of prematurity

**1.7 Background and Literature Review (maximum 1 page):**

In middle income countries including South Africa, retinopathy of prematurity (ROP) is emerging as a 'third epidemic' and is one of the most common causes of preventable blindness in preterm neonates.[1] Each year 16000 babies are at risk of ROP.[1] The prevalence of blindness due to ROP is 50000 worldwide.[2]

ROP affects premature infants of very low birth weight and causes a proliferative retinopathy. The immature retina is incompletely vascularised and is very susceptible to oxygen damage.[3] The incompletely vascularised retina produces vascular endothelial growth factor (VEGF). ROP is caused by rebound excessive VEGF production induced by the increased metabolic demand of the growing eye.[3]

Preventing retinal detachment or retinal scarring, and improving the visual outcome are the primary goals of ROP treatment.[4] Treatment modalities include pharmacologic blockade of VEGF, ablation of the peripheral avascular retina, and surgical intervention.[4]

Conventional laser treatment (CLT) of the avascular immature retina in infants with threshold disease is the conventional treatment modality.[3] The limitations of CLT include the irreversible and

extensive destruction of the peripheral retina, causing reduction in peripheral visual fields, the laborious nature of the treatment as well as the high level of training required to administer.[4] Premature babies are also exposed to the risks of relatively longer general anaesthesia. Complications of laser treatment include anterior segment ischemia and burns of the cornea, iris and cataract.[4] CLT can also induce cystoid macular oedema and myopia. According to the CRYO-ROP trial and ETROP trial the recurrence rates with conventional laser therapy are up to 50% for zone I disease and up to 20% for zone II posterior disease.[2] Therefore Zone 1 disease treated with CLT has a relatively high recurrence rate.

Aggressive posterior retinopathy of prematurity (AP-ROP) is a rare condition and is characterised by the prominence of plus disease, posterior location (Zone 1 or posterior zone 2) and poorly defined nature.[3] If not treated appropriately it often progress to stage 5 disease.[3] CLT is efficient in the treatment of most ROP cases. However, in AP-ROP, the disease often progress, despite extensive laser treatment.[5] Laser-treated eyes have a poor anatomical and functional outcome, with a high prevalence of retinal detachments.[5] CLT for AP-ROP is also technically and practically demanding due to opacities in the media and an extensive part of the central and peripheral retina is destroyed by laser treatment.[5]

Intravitreal bevacizumab (IVB) has been successfully used both as monotherapy and in combination with CLT, with/without vitrectomy.[2] The BEAT-ROP study has provided evidence of a significant reduction of retinal detachments in zone I ROP stage 3+ disease after IVB monotherapy.[2] IVB in zone 1 disease also showed a significantly lower recurrence rate compared to laser and significantly fewer complications (such as dragging of the macula and retinal detachments).[2] In eyes with zone II disease, there was no significant difference in recurrence rates between the treatment groups.[2] Development of peripheral retinal vessels continued after treatment with IVB, but conventional laser therapy led to permanent destruction of the peripheral retina.[2] The timing of recurrence was much later in subjects treated with IVB (16 weeks compared to 6 weeks).[4] In very mild stage 3+ ROP that might regress spontaneously, IVB averts the complications of CLT. Furthermore, IVB allows for the successful treatment of very extensive stage 3+ ROP, both type 1 (standard) and type 2 (AP-ROP).[2]

The findings of the BEAT-ROP study support a change in policy regarding treatment for AP-ROP. However, there is not much evidence based guidelines available concerning the treatment of AP-

ROP with IVB. Therefore, further studies are needed to analyse the outcome of patients diagnosed with AP-ROP and treated with IVB.

1.8 **Key References:** *(Give approximately 5 key references)*


1. Visser L, Singh R, Young M, Lewis H, McKerrow N. Guideline for the prevention, screening and treatment of retinopathy of prematurity (ROP). South African Med J. 2013;103:116–25.
2. Mintz-Hittner HA, Kennedy KA, Chuang AZ. Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. N Engl J Med. 2011; 364(7):603–15.
3. Kanski, JJ, Bowling, B. Clinical ophthalmology. A Systematic Approach. 7th ed. Edinburgh:Saunders Elsevier; 2011. p. 573-5.
4. Yanoff, M, Duker, JS. Ophthalmology, 4th ed. Edinburgh: Elsevier; 2013. p. 535-9.
5. Spandau U, Tomic Z, Ewald U, Larsson E, Åkerblom H, Holmström G. Time to consider a new treatment protocol for aggressive posterior retinopathy of prematurity? Acta Ophthalmol. 2013;91:170–5.


## 2. PLAN OF INVESTIGATION FOR STUDY

* In the case of Higher Degrees, please state name and School of person consulted regarding the design:

| | | | | |
|---|---|---|---|---|
| **2.1 Is this a retrospective chart review with no human contact?** | Yes | ✓ | No | |
| **2.2 Is this a study of stored tissue?** | Yes | | No | ✓ |
| **2.3 Are host genetic factors being studied?** | Yes | | No | ✓ |

2.4 **How many hours per week will the PI devote to this project?**

(Timetable the project in terms of the resources and time available) 3 hours per week

## 3. STATISTICAL PLANNING AND DATA ANALYSIS

| | | | | |
|---|---|---|---|---|
| 3.1 **Has this project been approved by a professional statistician?**<br><br>If No, please justify. | Yes | ✓ | No | |

3.2 **If answered "yes" to (3.1), provide the name of the statistician:** Prof. B Sartorius

**3.3 Please provide a brief overview of statistical and data analytic considerations, including:**

*How was the number of participants determined? Please include assumptions made in any power analysis (e.g. control incidence or mean and standard deviation of primary outcome variable, desired or anticipated effect of treatment or intervention, level of statistical significance and desired power), and list all planned statistical methods to be used. For descriptive studies list statistical operations to be performed.*

This is a descriptive study. Continuous variables will be summarized using mean and standard deviation (or media and interquartile range if data are skewed or outliers present). Categorical variables will be summarized using frequencies.

**3.4 For *qualitative* studies**: What is the framework/approach to be used for analysis of the data?

**4. PARTICIPANTS IN THE STUDY**

| | | | | | | |
|---|---|---|---|---|---|---|
| **4.1 Is this a multi-national study?**<br><br>(*If yes, state collaborating countries)* | Yes | | | No | ✓ | |

**4.2 List all sites in South Africa in which the project will be carried i.e. geographic location (e.g. KwaZulu-Natal) and type of place (e.g. hospital, clinic, schools, community etc).**

Geographic location: KwaZulu-Natal, Durban

Type of place: Inkosi Albert Luthuli Central Hospital

| **4.3 Source:** *(Please indicate number per group)* | Inpatients | Outpatients | Volunteers |
|---|---|---|---|
| | ✓ | | |

| | | | | | |
|---|---|---|---|---|---|
| **4.4 Age (human studies)** *(Please indicate number per group)* | Neonates (<28 days) ✓ | Infants (1-11 month) ✓ | Children (1-12 years) | Adolescent (13-17 years) | Adults |

| | | | | | |
|---|---|---|---|---|---|
| **4.5 Is there a control group(s)?** | Yes | | No | ✓ | |

**4.6 Demographic profile of participants** *(please tick ALL appropriate boxes below.)*

4.6.1 Gender: Female ✓ Male ✓

4.6.2 Population Group: Black ✓ Coloured ☐ Indian ✓ White ✓

4.6.3 Language Group/s: Specify…… Zulu, English, Afrikaans ……

**4.7 Describe the recruitment process in detail for all groups**. Retrospective chart review

| | | | | | | |
|---|---|---|---|---|---|---|
| **4.8 Will incentives be offered to facilitate recruitment?** (*If yes, describe in detail*) | Yes | | No | | N/A | ✓ |
| **4.9 Will participants be reimbursed in some way for participation?** (*If yes, describe in detail*) *See SA DoH Guidelines on BREC Website* | Yes | | No | | N/A | ✓ |

| | | | | | | |
|---|---|---|---|---|---|---|
| **4.10 Will reimbursement for participants and investigators be in accordance with:** *(If no, please explain)*<br><br>• Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa: Department of Health (2006) and;<br>• Ethics in Health Research: Principles, Structures and Processes: (2004)?<br>• Current SA DoH Guidance on reimbursement (*See BREC website*) | Yes | | No | | N/A | ✓ |
| **4.11 Will participants be insured against research related injury?**<br><br>*(If yes, please provide details; If no, please provide rationale)*<br>*Mandatory for Clinical Trials* | Yes | | No | | N/A | ✓ |

**4.12 List in detail the inclusion and exclusion criteria.**

Inclusion criteria:

- Premature/Low birth weight neonates that presented/were born at IALCH since 2011, that were diagnosed with AP-ROP and treated with intravitreal bevacizumab.
- Defaulters or patients that were not followed up for long enough to complete the treatment process were included for statistical purposes.

Exclusion criteria:

- Only patients that didn't meet the inclusion criteria were excluded.

## 5. POTENTIAL RISKS OR DISCOMFORT

| | | | | | |
|---|---|---|---|---|---|
| **5.1 Can the project have any potential risks or discomfort on participants, members of the public, researchers, field staff or the physical environment?** | Yes | | No | ✓ | |

5.2 If "yes" to (6.1) indicate, for each study group/arm, the potential additional risks as follows:
5.2.1 Biological risks
5.2.2 Psychological risks
5.2.3 Social Risks
5.2.4 Legal risks
5.2.5 Financial risks
5.2.6 Other risks

5.3 Please detail steps that will be taken to minimise the risks indicated above:
5.3.1 Biological risks
5.3.2 Psychological risks
5.3.3 Social Risks
5.3.4 Legal risks
5.3.5 Financial risks
5.3.6 Other risks

## 6. INFORMED CONSENT: GIVEN TO PARTICIPANTS

See SAMPLE INFORMATION SHEET AND CONSENT FORM ON UKZN BREC WEBSITE at
*http://research.ukzn.ac.za/Libraries/Notices2011/BREC_Informed_consent_form_sflb.sflb.ashx*

Other consent forms are acceptable provided that they contain at least the essential elements outlined in the current UKZN BREC Terms of Reference (ToR) and Standard Operating Procedures (SoP) available at
*http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx*

If necessary, information sheets and consent forms, after ethics approval of the English version, must be translated into appropriate local languages and submitted to BREC for further approval prior to implementation, with a copy of the translator's certificate, and back translations if applicable.

The correct and complete contact details for the UKZN Biomedical Research Ethics Committee should be in the information sheets and consent forms as follows:

BIOMEDICAL RESEARCH ETHICS ADMINISTRATION
Research Office, Westville Campus
Govan Mbeki Building
University of KwaZulu-Natal
Private Bag X 54001, Durban, 4000
KwaZulu-Natal, SOUTH AFRICA
Tel: 27 31 2602486 - Fax: 27 31 2604609
Email: BREC@ukzn.ac.za

**7. DECLARATION OF PRINCIPAL INVESTIGATOR**

Conflict of Interest:

I declare that all potential conflicts of interest regarding my application for ethics approval to conduct this study have been declared in accordance with UKZN and BREC Terms of Reference and Standard Operating Procedures.

**Undertaking:**

I understand and accept that I will be required to submit a yearly recertification application, failing which authorisation to continue the study lapses.
I undertake to request permission for any changes/amendments to the study from BREC in advance of implementing any such changes, unless they are emergencies required to prevent harm or save life. In such cases BREC must be notified urgently.

I agree to provide monitoring data if and when required.

I expect the project to be completed by **DATE**.....31 December 2017

I agree to abide by the guidance contained in the SA Department of Health (2004) Ethics in Health Research: Principles, structures and processes and the (2006) South African Good Clinical Practice Guidelines and the current UKZN Biomedical Research Ethics Committee Terms of Reference and Standard Operating Procedures. These are available at *http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx*

I understand and accept that all information pertaining to this application is a true reflection of the project proposed and I take full responsibility should there be any transgression.

**SIGNATURE OF PRINCIPAL INVESTIGATOR**.....

**FULL NAME OF PRINCIPAL INVESTIGATOR**....Thomas Johannes Tolan

**DATE**.....22/11/2016.....

**8. DECLARATION AND APPROVAL FROM SUPERVISOR AND CO-SUPERVISOR (if applicable)**
*(I HAVE READ AND CHECKED THE PROPOSAL AND IT IS READY FOR SUBMISSION;*

Remarks:

**SIGNATURE OF SUPERVISOR** .....

**FULL NAME OF SUPERVISOR**.....L. VISSER.....

**DATE**.....22/11/2016.....

**SIGNATURE OF CO-SUPERVISOR** .....N.A.....

**FULL NAME OF CO-SUPERVISOR**.....

**DATE**.....

**If applicable, attach a signed copy of the Supervision Agreement between the student, supervisor and any co-supervisor.**

**9. DECLARATION AND APPROVAL OF LINE MANAGER**
*(Must include verification of interdepartmental agreements and co-operation)*

Remarks:

**SIGNATURE OF LINE MANAGER** .....

**FULL NAME OF LINE MANAGER** L. VISSER

**DATE** 22/11/2014

**NB: If applicant is ACADEMIC LEADER/DEAN/HOS, the ACADEMIC LEADER'S/DEAN'S/HOS's Line Manager (DVC) must sign.**

**SIGNATURE OF ACADEMIC LEADER's/ HOS's/DEAN's Line Manager**.....

**FULL NAME OF ACADEMIC LEADER's, HOS's/DEAN's Line Manager**.....

**DATE**.....

# Appendix 2: Ethical approvals

## GCP certificate

NOVARTIS

**CERTIFICATE OF COMPLETION**

This is to certify that

Thomas Johannes Jordaan

HPCSA Membership No.: MP0597694

Has successfully completed the course entitled

**AN INTRODUCTION TO GOOD CLINICAL PRACTICE**

With 94%

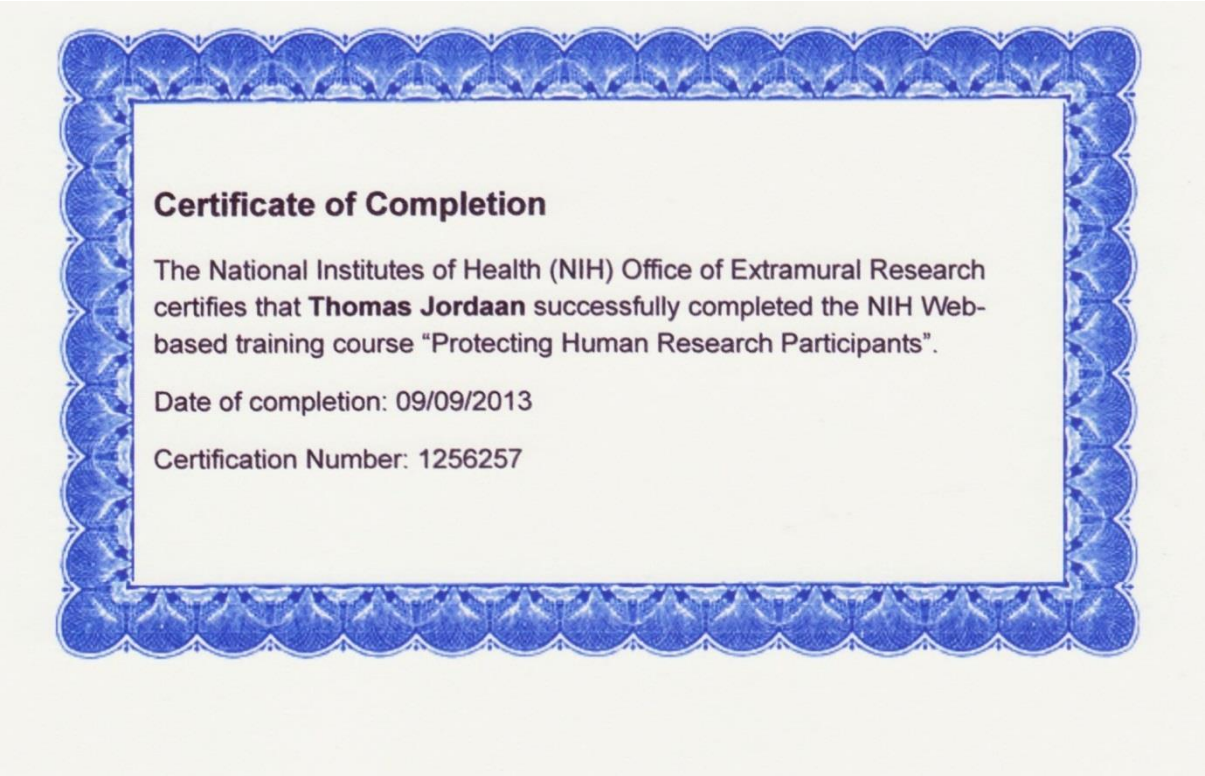
The HPCSA approved CPD reference is as follows:
MDB015/283/04/2014 Level 2: 12 points (Ethical=12)

SACRA/GCP/80/2013

Date: 05 APR 2014

Course Facilitator

## National institute of health certification



**Certificate of Completion**

The National Institutes of Health (NIH) Office of Extramural Research certifies that **Thomas Jordaan** successfully completed the NIH Web-based training course "Protecting Human Research Participants".

Date of completion: 09/09/2013

Certification Number: 1256257

# Ethics committee approval

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

23 December 2016

Dr Thomas Johannes Jordaan
113 Eleventh Avenue
Morningside
Durban
4001
tommiejordaan@yahoo.com

**PROTOCOL: Outcomes following intravitreal bevacizumab for aggressive posterior retinopathy of prematurity at a tertiary institution (213574211). REF: BE008/15**

**EXPEDITED APPLICATION**

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application received on 17 December 2014.

The study was provisionally approved pending appropriate responses to queries raised. Your response received on 13 December 2016 to BREC letter dated 17 August 2016 have been noted by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given full ethics approval and may begin as from 23 December 2016.

This approval is valid for one year from 23 December 2016. To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be **RATIFIED** by a full Committee at its next meeting taking place on 14 **February 2017.**

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely

Professor Joyce Tsoka-Gwegweni
Chair: Biomedical Research Ethics Committee

cc: Postgraduate Office
cc: yissen@ukzn.ac.za

Biomedical Research Ethics Committee
Professor J Tsoka-Gwegweni (Chair)
Westville Campus, Govan Mbeki Building
Postal Address: Private Bag X54001 Durban 4000
Telephone: +27 (0) 31 260 2435 Facsimile: +27 (0) 31 260 4609 Email: brec@ukzn.ac.za

# Appendix 3: Permission from medical manager

health
Department:
Health
**PROVINCE OF KWAZULU-NATAL**

Inkosi Albert Luthuli Central Hospital
Ethekwini Health District
Office of the Medical Manager
Private Bag X 03, Mayville, 4058
800 Bellair Road, Mayville, 4058
Tel.: 031 240 1059,
Fax.: 031 240 1050
Email.:ursulanun@ialch.co.za
www.kznhealth.gov.za

Reference: BE008/15
Enquiries: Medical Management

30 July 2015

Dr T J Jordaan
Department of Opthalmology
IALCH

Dear Dr Jordaan

**RE: PERMISSION TO CONDUCT RESEARCH AT IALCH**

I have pleasure in informing you that permission has been granted to you by the Medical Manager to conduct research on: **Outcomes following intravitreal bevacizumab for aggressive posterior retinopathy of prematurity at a tertiary institution**

Kindly take note of the following information before you continue:

1. Please ensure that you adhere to all the policies, procedures, protocols and guidelines of the Department of Health with regards to this research.
2. This research will only commence once this office has received confirmation from the Provincial Health Research Committee in the KZN Department of Health.
3. Kindly ensure that this office is informed before you commence your research.
4. The hospital will not provide any resources for this research.
5. You will be expected to provide feedback once your research is complete to the Medical Manager.

Yours faithfully

.....
**Dr M Letebele**
**Medical Manager**

# Appendix 4: Provincial health research committee approval

health
Department:
Health
**PROVINCE OF KWAZULU-NATAL**

Inkosi Albert Luthuli Central Hospital
Ethekwini Health District
Office of the Medical Manager
Private Bag X 03, Mayville, 4058
800 Bellair Road, Mayville, 4058
Tel.: 031 240 1059,
Fax.: 031 240 1050
Email.:ursulanun@ialch.co.za
www.kznhealth.gov.za

30 July 2015

Dr T J Jordaan
Department of Ophthalmology
UKZN

Dear Dr Jordaan

**Re: Approved Research: Ref No: BE008/15: Outcomes following intravitreal bevacizumab for aggressive posterior retinopathy of prematurity at a tertiary institution.**

As per the policy of the Provincial Health Research Committee (PHRC), you are hereby granted permission to conduct the above mentioned research once all relevant documentation has been submitted to PHRC inclusive of Full Ethical Approval.

Kindly note the following.

1. The research should adhere to all policies, procedures, protocols and guidelines of the KwaZulu-Natal Department of Health.
2. Research will only commence once the PHRC has granted approval to the researcher.
3. The researcher must ensure that the Medical Manager is informed before the commencement of the research by means of the approval letter by the chairperson of the PHRC.
4. The Medical Manager expects to be provided feedback on the findings of the research.
5. Kindly submit your research to:

   The Secretariat
   Health Research & Knowledge Management
   330 Langaliballe Street, Pietermaritzburg, 3200
   Private Bag X9501, Pietermaritzburg, 3201
   Tel: 033395-3123, Fax 033394-3782
   Email: hrkm@kznhealth.gov.za

Yours faithfully

.....
**Dr M Letebele**
**Medical Manager**

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

Health Research & Knowledge Management sub-component
10 – 103 Natalia Building, 330 Langalibalele Street
Private Bag x9051
Pietermaritzburg
3200
Tel.: 033 – 3953189
Fax.: 033 – 394 3782
Email.: hrkm@kznhealth.gov.za
www.kznhealth.gov.za

**Reference : HRKM 219/15**
**NHRD: KZ_RP201511_935**
**Enquiries : Mr X Xaba**
**Tel : 033 – 395 2805**

Dear Dr T. Jordaan

**Subject: Approval of a Research Proposal**

1. The research proposal titled **'Outcomes following intravitreal bevacizumab for aggressive posterior retinopathy of prematurity at a tertiary institution'** was reviewed by the KwaZulu-Natal Department of Health.

   The proposal is hereby **approved** for research to be undertaken at Inkosi Albert Luthuli Central Hospital.

2. You are requested to take note of the following:
   a. Make the necessary arrangement with the identified facility before commencing with your research project.
   b. Provide an interim progress report and final report (electronic and hard copies) when your research is complete.

3. Your final report must be posted to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to hrkm@kznhealth.gov.za

For any additional information please contact Mr X. Xaba on 033-395 2805.

Yours Sincerely

Dr E Lutge
Chairperson, Health Research Committee
Date: 28/08/15

# Appendix 5: Supervisor report

**SUPERVISOR'S REPORT**

**PLEASE NOTE;** This must essentially be a descriptive and non-evaluative report

1. **Candidate:** Dr. T. J. Jordaan ..... **Student no:** 21357421 1.....
2. **Registered title:** Outcomes following intravitreal bevacizumab for aggressive posterly located retinopathy of prematurity at a tertiary institution.
3. **Reference number:** BE 008/15
4. **Approved by Postgraduate Education Committee:** Yes
5. **Approved by Biomedical Research Ethics Committee:** Yes
6. **Supervision history:** I supervised the whole process Yes X No ___
   1. If no, I took over from another supervisor : (date)
   2. Describe the stage at which the student was at that time:
7. **Schedule of supervision (describe):** Monthly
8. **Adherence of the candidate to the schedule (describe):** Good
9. **Level of guidance or assistance given (mark appropriate column)**

| Step | No assistance | Minimal assistance | Average assistance | Massive assistance |
|---|---|---|---|---|
| Formulation of research topic | | | ✓ | |
| Developing research proposal | | | ✓ | |
| Literature search | | ✓ | | |
| Defining theoretical basis | | | ✓ | |
| Choosing research design | | | ✓ | |
| Appropriate referencing | | | ✓ | |
| Data collection instruments | | ✓ | | |
| Conducting field work | ✓ | | | |
| Developing the argument | | | ✓ | |
| Solution of research problems | | | ✓ | |
| Data analysis | | | ✓ | |

| | | | | |
|---|---|---|---|---|
| Expression, style and presentation | | | ✓ | |

**10. Describe the response of the candidate to suggestions or recommendations**

Obliging

**11. Describe any resource constraints which influenced the candidate**

None as retrospective

**12. Any further information which is relevant** N.A

**13. I saw/~~did not see~~ the final version of the report that was handed in**

**14. I approve of/~~do not approve of~~ the final version that was submitted**

**15. I am satisfied that, to the best of my knowledge, there is no plagiarism in the report.**
**Yes** X **No** _____

**Supervisor:** L. VISSER

**Signature:** _____ **Date:** 7/6/2017

**Co-supervisor:** _____

**Signature:** _____ **Date:** _____

# Appendix 6: The Guidelines for Authorship for African Vision and Eye Health Journal



## Structure and style of your original research article

The page provides an overview of the structure and style of your original research article to be submitted to the *African Vision and Eye Health*. An original article provides an overview of innovative research in a particular field within or related to the focus and scope of the journal, presented according to a clear and well-structured format (between 3500 and 7000 words with a maximum of 60 references). Compulsory as a supplementary file: Ethical clearance letter/certificate.

When presenting your article in English. Please use British English, that is, according to the *Oxford English Dictionary*. Avoid Americanisms (e.g. use 's' and not 'z' spellings). Consult the *Oxford English Dictionary* when in doubt and remember to set your version of Microsoft Word to UK English.

Language: Manuscripts must be written in British English or French.

Line numbers: Insert continuous line numbers.

Font type: Palatino

Symbols font type: Times New Roman

General font size: 12pt

Line spacing: 1.5

Headings: Ensure that formatting for headings is consistent in the manuscript.

First headings: normal case, bold and 14pt

Second headings: normal case, underlined and 14pt

Third headings: normal case, bold and 12pt

Fourth headings: normal case, bold, running-in text and separated by a colon.

Our publication system supports a limited range of formats for text and graphics. Text files can be submitted in the following formats only:

Microsoft Word (.doc): We cannot accept Word 2007 DOCX files. If you have created your manuscript using Word 2007, you must save the document as a Word 2003 file before submission.

Rich Text Format (RTF) documents uploaded during Step 2 of the submission process. Users of other word processing packages should save or convert their files to RTF before uploading. Many free tools are available that will make this process easier.

 For full details on how to ensure your manuscript adheres to the house style, click here.

The structure and style of your original article

## Page 1

The format of the compulsory cover letter forms part of your submission, is on the first page of your manuscript and should always be presented in English. You should provide all of the following elements:

Full author details: Provide title(s), full name(s), position(s), affiliation(s) and contact details (postal address, email, telephone and cellular number) of each author.

Corresponding author: Identify to whom all correspondence should be addressed.

Summary: Lastly, a list containing the number of words, pages, tables, figures and/or other supplementary material should accompany the submission.

## Page 2 and onwards

Title: The article's full title should contain a maximum of 95 characters (including spaces).

Abstract: The abstract, written in English, should be no longer than 250 words and must be written in the past tense. The abstract should give a succinct account of the objectives, methods, results and significance of the matter. The structured abstract for an Original Research article should consist of six paragraphs labelled Background, Aim, Setting, Methods, Results and Conclusion. The journal can translate into French if this is difficult for you.

Background: Summarise the social value (importance, relevance) and scientific value (knowledge gap) that your study addresses.

Aim: State the overall aim of the study.

Setting: State the setting for the study.

Methods: Clearly express the basic design of the study, and name or briefly describe the methods used without going into excessive detail.

Results: State the main findings.

Conclusion: State your conclusion and any key implications or recommendations.

Do not cite references and do not use abbreviations excessively in the abstract.

The following headings serve as a guide for presenting your research in a well-structured original article. As an author you should include all first-level headings, but subsequent headings (second- and third-level headings) can be changed.

Introduction (first-level heading)
The introduction must contain your argument for the social and scientific value of the study, as well as the aim and objectives:

Social value: The first part of the introduction should make a clear and logical argument for the importance or relevance of the study. Your argument should be supported by use of evidence from the literature.

Scientific value: The second part of the introduction should make a clear and logical argument for the originality of the study. This should include a summary of what is already known about the research question or specific topic, and should clarify the knowledge gap that this study will address. Your argument should be supported by use of evidence from the literature.

Conceptual framework: In some research articles it will also be important to describe the underlying theoretical basis for the research and how these theories are linked together in a conceptual framework. The theoretical evidence used to construct the conceptual framework should be referenced from the literature.

Aim and objectives: The introduction should conclude with a clear summary of the aim and objectives of this study.

Research methods and design (first-level heading)
The methods should include:

Study design (second-level heading): An outline of the type of study design.

Setting (second-level heading): A description of the setting for the study; for example, the type of community from which the participants came or the nature of the health system and services in which the study is conducted.

Study population and sampling strategy (second-level heading): Describe the study population and any inclusion or exclusion criteria. Describe the intended sample size and your sample size calculation or justification. Describe the sampling strategy used. Describe in practical terms how this was implemented.

Intervention (if appropriate) (second-level heading): If there were intervention and comparison groups, describe the intervention in detail and what happened to the comparison groups.

Data collection (second-level heading): Define the data collection tools that were used and their validity. Describe in practical terms how data were collected and any key issues involved, e.g. language barriers.

Data analysis (second-level heading): Describe how data were captured, checked and cleaned. Describe the analysis process, for example, the statistical tests used or steps followed in qualitative data analysis.

Ethical considerations (second-level heading): Approval must have been obtained for all studies from the author's institution or other relevant ethics committee and the institution's name and permit numbers should be stated here.

Results (first-level heading)
Present the results of your study in a logical sequence that addresses the aim and objectives of your study. Use tables and figures as required to present your findings. Use quotations as required to establish your interpretation of qualitative data.

All units should conform to the SI convention and be abbreviated accordingly. Metric units and their international symbols are used throughout, as is the decimal point (not the decimal comma).

Discussion (first-level heading)
The discussion section should address the following four elements:

Key findings: Summarise the key findings without reiterating details of the results.

Discussion of key findings: Explain how the key findings relate to previous research or to existing knowledge, practice or policy.

Strengths and limitations: Describe the strengths and limitations of your methods and what the reader should take into account when interpreting your results.

Implications or recommendations: State the implications of your study or recommendations for future research (questions that remain unanswered), policy or practice. Make sure that the recommendations flow directly from your findings.

Conclusion (first-level heading)
Provide a brief conclusion that summarises the results and their meaning or significance in relation to each objective of the study.

Acknowledgements (first-level heading)
If, through your study, you received any significant help in conceiving, designing or carrying out the work, or received materials from someone who did you a favour by supplying them, you must acknowledge their assistance and the service or material provided. Authors should always acknowledge outside reviewers of their drafts and any sources of funding that supported the research.

Competing interests (second-level heading): A competing interest exists when your interpretation of data or presentation of information may be influenced by your personal or financial relationship with other people or organisations that can potentially prevent you from executing and publishing unbiased research. Authors should disclose any financial competing interests but also any non-financial competing interests that may cause them embarrassment were they to become public after the publication of the manuscript. Where an author has no such competing interests, the listing will read as follows: 'The authors declare that they have no financial or personal relationship(s) that may have inappropriately influenced them in writing this article.'

Authors' contributions (second-level heading): This section is necessary to give appropriate credit to each author, and to the authors' applicable institution. The individual contributions of authors should be specified

with their affiliation at the time of the study and completion of the work. An 'author' is generally considered to be someone who has made substantive intellectual contributions to a published study. Contributions made by each of the authors listed can follow the example below (please note the use of authors' initials):

J.K. (University of Pretoria) was the project leader, L.M.N. (University of KwaZulu-Natal) and A.B. (Stellenbosch University) were responsible for experimental and project design. L.M.N. performed most of the experiments. P.R. (Cape Peninsula University of Technology) made conceptual contributions and S.T. (University of Cape Town), U.V. (University of Cape Town) and C.D. (University of Cape Town) performed some of the experiments. S.M. (Cape Peninsula University of Technology) and V.C. (Cape Peninsula University of Technology) prepared the samples and calculations were performed by C.S. (Cape Peninsula University of Technology).

References (first-level heading)
Begin the reference list on a separate page, and give no more than 60 references in all. The *African Vision and Eye Health* uses the Vancouver referencing style, details of which can be downloaded from the journal website. Note: No other style will be permitted.

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Guidelines for Math

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Fonts: Please use standard (UNIcode) fonts such as Palatino, Times New Roman, Helvetica and Symbol. Fonts that have not been embedded will usually be replaced by Courier, resulting in character loss or realignment.

Creatives: Please supply images as the size intended for final publication. Resizing of images is time consuming and can result in loss of quality.

### Types of articles published by the *African Vision and Eye Health*

Most articles published by the *African Vision and Eye Health* follow a specific format, as listed below:

Original research articles: These are reports on complete, comprehensive pieces of original research dealing with the exploration of issues and experiences relating to, and supporting, opthamology and optometrist best-practice development through research learning and problem-based knowledge sharing across the African continent. (Maximum 7000 words; 60 references.) Compulsory as a supplementary file: Ethical clearance letter/certificate.

Review articles: The review article informs a broad readership about fields in which there have been recent, important advances of immense, fundamental significance and highlights unresolved questions and future directions (between 2500 and 4000 words; abstract optional but compulsory for long reviews).

Notes: Short, Research and Technical Notes.

Occasionally there may be a Thesis Abstract, Book Reviews, Matters Arising or Letters to the Editor. These items are per invitation from the Editor-in-Chief.

References: Begin the reference list on a separate page. The *African Vision and Eye Health* uses the Vancouver referencing style. Note: no other style will be permitted.

Submit: New submission | Revised submission | Thesis abstract

Learn how to ensure your manuscript adheres to the AOSIS Publishing house style.

The submission process can be interrupted at any time; when users return to their journal's personalised section, they can continue from where they left off.

Language usage ↑

## General elements

Quotations: Use single quotation marks for quotations. For quotations within quotations, use double quotation marks. Quotations of more than 30 words are to be indented. Do not use quotation marks for indented quotations unless it is direct speech (e.g. interviewee responses).

En dashes and hyphens: Use an en dash (i.e. extended hyphen that can be found in the Insert box under Symbols in Microsoft Word) in ranges of numbers and dates. Use hyphens only for words that are hyphenated.

Dates: Format dates as '02 October 2006', except at the beginning of sentences where numerals and dates should either be spelt out or the sentence should be rearranged.

Percentage: The per cent symbol (%) is used in conjunction with all numbers (e.g. 12%). Numbers that have been written out will appear with 'per cent' (e.g. five per cent). 'Percentage' is used in a general sense.

Numbers: Numbers from one to nine must be written out. Numbers from 10 onwards, must be used as numerals, except at the beginning of a sentence.

Spacing and punctuation: There should be one space (and not two) between sentences; one space before unit terms (e.g. 5 kg, 5 cm, 5 mmol, 5 days, 5 °C, etc.), but no space before the percentage symbol (%). Thousands and millions are marked with a space and *not* a comma (e.g. 1000, 1 000 000). Ranges are expressed with an extended hyphen (i.e. en dash), not with a short hyphen (e.g. 1990–2000).

Units: The use of units should conform to the SI convention and be abbreviated accordingly. Metric units and their international symbols are used throughout, as in the decimal point (not the decimal comma), and the 24-hour clock.

Foreign language: Foreign language words should be italicised, unless these words are part of normal usage. Consult the Oxford English Dictionary if in doubt.

Acronyms: If a phrase with an established acronym or abbreviation is used and appears more than five times in your article, please include the acronym or abbreviation in brackets after first mention of the phrase, and then use the acronym or abbreviation only. Please note that you should not define acronyms or abbreviations in any of your headings. If either has been used in your abstract, you need to define them again on their first usage in the main text.

## Sensitive and political terms

Race and ethnicity: Try to avoid terms such as 'Blacks' and 'Whites' (please note the use of uppercase letters); use instead 'Black *people'*, 'White *people'*, etc. 'Caucasian', 'Mongoloid', 'Negroid', etc. are generally to be avoided except in human population studies. 'Mixed race' is preferable to 'half-caste' or 'Coloured'.

Disabilities: Avoid using 'the disabled', 'the handicapped', and instead use 'people with disabilities not 'the disabled' or 'people with learning difficulties', not 'mentally handicapped'.

Disease

Avoid health-determined categorisation.

Use 'people with diabetes'; not 'diabetics'.

Use 'people with cancer'; not 'cancer sufferers'.

Use 'sexually transmitted infection (STI)' and not 'sexually transmitted disease (STD)'.

Avoid phrasing that dehumanises a patient. Many authors use case (instance of a disease) when they mean patient (i.e. the person or individual who is ill with the (disease).

AIDS

Ensure that 'AIDS' is used for the disease and 'HIV' for the virus, e.g. do not use 'AIDS carrier', 'AIDS positive', 'AIDS virus' or 'catching AIDS or HIV/AIDS' (avoid using the solidus here).

'AIDS sufferer/victim' is inappropriate; use 'people with AIDS'.

Refer to 'people who practise high-risk activities' and not '*high-risk groups'.*

The expression 'full-blown AIDS' is unnecessary if the correct distinction has been made between HIV and AIDS.

Male versus Female

'Male' and 'female' are *adjectives*, so be careful to use them as such (i.e. a *male* patient and a *female* frog, but a 35-year-old *man*, a French *woman* and a group of 25 *men* and 35 *women*).

Sexuality: Avoid the terms '*homosexual activities*' (if achievable within the manuscript's context, specify which activity is being referred to, especially when dealing with medical research.) Avoid using '*homosexuals*' (specify homosexual men or homosexual women).

Gender: Use gender neutral nouns. Avoid the use of 'man' if not specifically referring to men; for example:

for 'man' use 'humans'

for 'man-kind' use 'the human race'

for 'man-power' use 'workforce'

for 'man-made fibre' use 'synthetic fibre'

'He/she', 'him/her' and 'his/hers': For 'he/she', 'him/her' and 'his/hers' rather use 'he or she', 'her or him', 'his or hers' (without a solidus) or change to plural 'they'. Use inclusive pronouns: use 'he or she', or rephrase the sentence (rephrasing to the plural form often works):

✗ … *Any observer* of changes in publishing technology will perceive that *he* has need of…

✓ … *Observers* of… will perceive that *they* have…

Beware of referring to people with stereotypical pronouns (e.g. 'the doctor treated *his* patient'; 'the secretary tidied *her* desk').

Geography

The terms *Third World*, *poor countries* and *underdeveloped countries* should be avoided.

*Developing* or *non-developed country/society* is better, but it is best to specify countries or regions instead.

*Western society* and *Western World* should only be used in relation to geography; otherwise, use *developed world/society* or, even better, specify the countries themselves or the region.

## Tables, figures and photographs ↥

In Step 4 of the online submission process, upload all tables, figures, images, and supplementary files. Tables should be saved and uploaded as separate Excel (.xls) files with no more than 10 figures and tables in total per article. Ensure that all personal identifying information is removed from the supplementary files as indicated in the provided instructions. All captions should be provided together on a separate page. Tables and figures should use numerical numbers.

Organise your visual presentation: Once you have read through the analyses and decided how best to present each table or figure, think about how you will arrange them within the article. The analyses should tell a story' that leads the reader through the steps needed to logically answer the question(s) that you as author are posing

in the Introduction. The order in which you present the results can be as important in convincing the readers as what you actually are saying in the text.

How to refer to tables and figures in the text: Every figure and table included in the paper *must* be referred to in the body of the text. Use sentences that draw the reader's attention to the relationship or trend you wish to highlight, referring to the appropriate figure or table only in parenthesis e.g.:

Germination rates were significantly higher after 24 h in running water than in controls (Figure 4).

DNA sequence homologies for the purple gene from the four congeners (Table 1) show high similarity, differing by at most 4 base pairs. (Avoid sentences that give no information other than directing the reader to the figure or table, e.g. Table 1 shows the summary results for male and female heights at Bates College.)

Abbreviation of the word 'Figure': When referring to a figure in the text, the word 'figure' is never abbreviated as 'Fig.'; the same rule applies to the usage of 'table'. Both words are spelled out completely in descriptive legends.

How to number tables and figures: Figures and tables are numbered independently, in the sequence in which you refer to them in the text, starting with Figure 1 and Table 1. If, in revision, you change the presentation sequence of the figures and tables, you must renumber them to reflect the new sequence.

The acid test for tables and figures: Any table or figure you present must be clear, well-labelled, and described by its legend to be understood by your intended audience without reading the results section. That is, it must be able to stand alone and be interpretable. Overly complicated figures or tables may be difficult to understand in or out of context, so strive for simplicity whenever possible.

Descriptive legends or captions: To pass the acid test above, a clear and complete legend (sometimes called a caption) is essential. Like the title of the article itself, each legend should convey as much information as possible about what the table or figure intends to tell the reader:

the results that are being shown in the graph(s), including the summary statistics plotted

the organism studied in the experiment (if applicable)

a context for the results: the treatment applied or the relationship displayed, etc.

location (*only* if a field experiment)

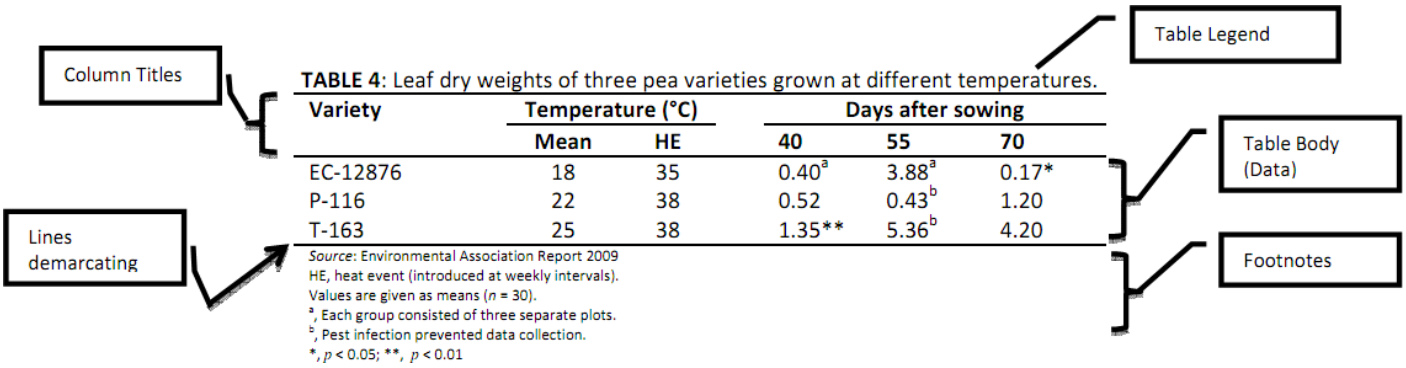
specific explanatory information needed to interpret the results shown (in tables, this is frequently done as footnotes)

culture parameters or conditions if applicable (temperature, media, etc.)

sample sizes and statistical test summaries, as they apply

Do not simply restate the axis labels with a 'versus' written in between.

Example: Figure 1: Height frequency (%) of White Pines (Pinusstrobus) in the Thorncrag Bird Sanctuary, Lewiston, Maine, before and after the Ice Storm of 1998. Before, $n$ = 137, after, $n$ = 133. Four trees fell during the storm and were excluded from the post-storm survey.




Note: Questions frequently arise about how much methodology to include in the legend, and how much results reporting should be done. For laboratory reports, specific results should be reported in the results text with a reference to the applicable table or figure. Other than culture conditions, methods are similarly confined to the Methods section.

## Footnotes to tables, figures and photographs

Do not introduce footnotes in the body of the article. Footnotes should be used as follows:

Copyright and permissions to reproduce should be clearly stated.

Notes about the table as a whole can be left unlinked (i.e. no linking letters or numbers or symbols) or linked to, for example, a relevant column heading.

Notes about specific parts of the table should be linked using superscript lower case letters (preferred), superscript numbers or symbols.

If lower case letters are used, it could be confused with the table data; use symbols or numbers instead.

Do not make use of superscript numbers in parentheses (brackets).

If an abbreviation is mentioned for the first time in a table (e.g. 'CE' in Table 1), it must be defined in a footnote to that table, (e.g. HE, Heat event (introduced at weekly intervals).

Asterisk footnotes are reserved for probability values in tables and usually signify the following values: *, $p \leq 0.05$; **, $p \leq 0.01$; ***, $p \leq 0.001$. The asterisk is often used in mathematics and should therefore be avoided as a footnote symbol.

Footnote links should be placed after punctuation. The preferred order of footnote symbols in tables (which should be superscripted) is †, ‡, §, ¶ (these are doubled if more footnotes are needed, e.g. ††).

When superscript numbers or letters are used in text, beware of potential confusion with other superscripts (e.g. 2 for 'squared').

Footnotes should be in the following order:

source notes

other general notes

notes on specific parts of the table (following the order in the table itself)

notes on level of probability

## Guidance on submitting creatives electronically

Supply your manuscript creatives  in one of the following three preferred formats:

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Colour or greyscale photographic images: 300dpi

Line art or combination images: 600/900dpi

We would recommend using this format for photographic images.

EPS: An EPS is essentially an envelope for holding text and images. Line art can be produced as an EPS (in Illustrator, for example). There are virtually no limits to scaling line art saved as an EPS. It can also contain TIFF images. However, please ensure that all fonts are embedded (that is, saved as outlines) and that line weights are not defined as hairline.

PDF: This format is, again, like an EPS in that it is an envelope for holding different kinds of images and line art. Great care should be taken to ensure that fonts are embedded and that original images are at the correct size and resolution before being saved as a PDF. It is possible to save or export as TIFF or EPS from most graphics applications, just as it is possible to save direct to a PDF from most graphics packages by using a postscript printer driver. PDF creation packages (e.g. Acrobat Distiller) are also now widely available.

Other file formats

JPEG: A JPEG compressed TIFF is acceptable as long as the degree of compression is moderate. It is better to use a JPEG for online images as a good quality image is achievable even with a high degree of compression.

GIF: A format suitable for images that contain few colours. Again, this should only be used for images intended for the web.

We cannot guarantee the quality of images supplied in other formats.

Colour:

*Greyscale, CMYK, RGB.*

Greyscale art should be saved in greyscale mode.

CyanMagentaYellowBlack are the base colours used during the printing process.

Any colour that is to appear in print must be in CMYK mode.

RedGreenBlue are the colours used by monitors and default scanner settings. Any colour that is to appear online must be in RGB mode.

### Guidelines for Math ↑

Set display equations in MathType. Each display equation should be in its own MathType object. Each MathType object should contain the entire equation, including final punctuation. The equation number should be set as Microsoft Word regular text, outside the MathType object, separated by either a tab or a space.

Set in-text (inline) math in Microsoft Word regular text. Exception: If in-text (inline) math has elements that should be stacked or have rules, circumflexes, arrows, or other accents spanning over more than one character, set in MathType as 'Inline Equation.'

If any characters cannot be found in Word's Symbol palette ('(normal text),' 'Times New Roman,' or 'Symbol'), please set in MathType.

No display equations are allowed in figure captions, table titles, or table footnotes. If a display equation occurs in a text footnote, it is best to recast it as inline math. There are a few journals with lengthy footnotes with style exceptions to this rule.

No numbered equations are allowed in table footnotes.

Display and/or numbered equations ARE allowed in table body, but must be 'inline' when converted to MathML equations.

## New submission

This page includes instructions for authors on how to make a submission to the *African Vision and Eye Health*. For details of how to prepare and submit a revised manuscript via the online manuscript submission system, please see the instructions for resubmission (after formal peer review).

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Cover page

Fromatting requirements

## Publication ethics

## Plagiarism

## Instructions on how the submission process work

### Submit original work to the *African Vision and Eye Health* ↑

We ask our authors to ensure that they submit original work that:

have been honestly carried out according to rigorous scientific standards that has not been obtained fraudulently or dishonestly, or fabricated or falsified

present an accurate account of the research performed and the results obtained and offer an objective discussion of the significance thereof

present sufficient detail and reference to public sources of information in order to permit peers to repeat the work if needed

report data accurately and never 'fudged', with any problematic data also treated accordingly

cite all relevant references; it is the duty of the author to check the references that are cited very carefully to ensure that the details are accurate and in the correct format

declare any (potential) conflicts of interest

do not claim originality if others have already reported similar work in part or as a whole

give credit to the work and findings of others that have led to your findings or influenced them in some way

identify any hazards inherent in conducting the research

do not contain plagiarised material or anything that is libellous, defamatory, indecent, obscene or otherwise unlawful and that the work does not infringe on the rights of others

provide all the statements required by the journal in order to prove that the experimental protocols were approved appropriately and that they meet all the guidelines of the agency involved, including obtaining informed consent where required if investigations have involved animals or human subjects

contain explicit permission of the individuals from whom information was privately obtained and that they have accompanying appropriate letters confirming permission to include this information , as may be acquired by journals

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Corresponding author: Identify to whom all correspondence should be addressed to.

Authors' contributions: Briefly summarise the nature of the contribution made by each of the authors listed.

Summary: Lastly, a list containing the number of words, pages, tables, figures and/or other supplementary material should accompany the submission.

Formatting requirements: Please use British English, that is, according to the Oxford English Dictionary. Avoid Americanisms (e.g. use 's' and not 'z'). Consult the Oxford English Dictionary when in doubt and remember to set your version of Microsoft Word to UK English.

Language: Manuscripts must be written in British English.

Line numbers: Insert continuous line numbers.

Font:

Font type: Palatino

Symbols font type: Times New Roman

General font size: 12pt

Line spacing: 1.5

Headings: Ensure that formatting for headings is consistent in the manuscript.

First headings: normal case, bold and 14pt

Second headings: normal case, underlined and 14pt

Third headings: normal case, bold and 12pt

Fourth headings: normal case, bold, running-in text and separated by a colon.

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Please read the following publication policy relating to retracting or correcting articles when needed:

Correcting the record

## Instructions on how the submission process work ↑

The authors of an article need to decide who the corresponding author will be that will take responsibility during the submission, peer review and editing processes. By submitting an article for publication you confirm that you are the corresponding/submitting author and that AOSIS will be communicating with you about the article.

Firstly, register or ensure you have an author account with the *African Vision and Eye Health*. Secondly, ensure your contact details are updated in your profile.

After you have logged in and clicked on Author, click on the link start a new submission to go to Step 1 of the five-step submission process (scroll down and click on the Next button on each screen to save your work and advance to the next screen):

Select the journal section and complete the submission checklist.

Upload submission file. Click on the Browse button and locate the file on your computer. When you have selected the file you wish to upload, click the Upload button. Review your submission (in a Word .doc) before sending it to the editors and ensure you have included your manuscript cover page.

Complete the manuscript metadata, author(s) details, manuscript title, manuscript abstract and keywords.

Upload either a separate cover page or other multiple supplementary file(s), such as large tables and photographs:

Click on the Browse button and locate the file on your computer.

Select the designation of your supplementary files (.eps, .xls).

When you have selected the file you wish to upload, click the Upload button. Note*: You have a limit of 15MB for a single file you upload*.

Repeat the process until all supplementary files have been uploaded. Note*: You can only upload 1 supplementary file at a time.*

Review your submission online in Step 5.

Click the Finish Submit button when you would like to complete the manuscript submission to the journal.

Support videos:

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# Appendix 7: Raw data

## Demographics summary:

| Patient nr. | Gender | Race | Year of birth | GA | BW | L/R eye | Indication for IVB | Zone 1 | Posterior Zone2 | Intervention |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Male | Indian | 2016 | 30 | 0.11 | L | AP-ROP | Stage 3+ | | B |
| | | | | | | R | AP-ROP | Stage 3PP | | B |
| 2 | Male | Black-African | 2015 | 32 | 0.96 | R | AP-ROP | | Stage 3+ | B |
| 3 | Male | Black-African | 2014 | 26 | 0.85 | L | AP-ROP | Stage 3+ | | B+C |
| | | | | | | R | AP-ROP | Stage 3+ | | B |
| 4 | Male | Black-African | 2014 | 29 | 1.35 | L | AP-ROP | N | | B+C |
| | | | | | | R | AP-ROP | N | | B |
| 5 | Female | Black-African | 2014 | 27 | 0.85 | L | S3Z1+ | Stage 3+ | | B |
| | | | | | | R | S3Z1+ | Stage 3+ | | B |
| 6 | Female | Black-African | 2013 | 29 | 1.12 | L | AP-ROP | N | | B |
| | | | | | | R | AP-ROP | N | | B |
| 7 | Male | Black-African | 2013 | 26 | 1 | L | S3Z1+ | Stage 3+ | | B |
| | | | | | | R | AP-ROP | Stage 2+ | | B |
| 8 | Female | Black-African | 2012 | 29 | 1.18 | L | AP-ROP | | Stage 3+ | B+C |
| | | | | | | R | AP-ROP | | Stage 3+ | B+C |
| 9 | Female | Black-African | 2012 | 28 | 0.74 | L | AP-ROP | Stage3+ | | B+P |
| | | | | | | R | AP-ROP | Stage3+ | | B+P |
| 10 | Female | Black-African | 2012 | 28 | 1.17 | L | AP-ROP | Stage 3+ | | B |
| | | | | | | R | AP-ROP | Stage 2+ | | B |
| 11 | Male | Indian | 2012 | 29 | 1.1 | L | AP-ROP | Stage 2+ | | B |
| | | | | | | R | AP-ROP | Stage 2+ | | B |
| 12 | Male | Black-African | 2012 | 29 | 0.89 | L | AP-ROP | Stage 2+ | | B |
| | | | | | | R | AP-ROP | Stage 2+ | | B |
| 13 | Female | Black-African | 2012 | 30 | 1.27 | R | Th | Stage 3+ | | B+C+P |
| 14 | Female | Black-African | 2012 | 29 | 1.2 | L | AP-ROP | N | | B |
| | | | | | | R | AP-ROP | N | | B+C+P |
| 15 | Female | White | 2012 | 24 | 0.82 | L | AP-ROP | Stage 2+ | | B |
| | | | | | | R | AP-ROP | Stage 2+ | | B |
| 16 | Female | Black-African | 2012 | 28 | 0.97 | L | AP-ROP | | Stage 2+ | B |
| | | | | | | R | AP-ROP | | Stage 2+ | B |
| 17 | Female | Black-African | 2011 | 31 | 1.065 | L | AP-ROP | Stage 1+ | | B |
| | | | | | | R | AP-ROP | Stage 1+ | | B |
| 18 | Male | Mixed race | 2011 | 29 | 1.1 | L | AP-ROP | Stage 1+ | | B |
| | | | | | | R | AP-ROP | Stage 1+ | | B |
| 19 | Female | Black-African | 2011 | 27 | 0.87 | L | AP-ROP | | Stage 3+ | B+C |
| | | | | | | R | AP-ROP | | Stage 3+ | B+C |
| 20 | Male | Indian | 2011 | 28 | 0.99 | L | AP-ROP | Stage 3+ | | B+C |
| | | | | | | R | AP-ROP | Stage 3+ | | B+C |
| 21 | Female | Black-African | 2011 | 29 | 1.1 | L | AP-ROP | Stage 3+ | | B+C |
| | | | | | | R | AP-ROP | Stage 3+ | | B+C |
| 22 | Female | Black-African | 2011 | 29 | 1.1 | L | AP-ROP | Stage 2+ | | B+C+P |
| | | | | | | R | AP-ROP | Stage 2+ | | B+C+P |
| 23 | Female | Black-African | 2011 | 28 | 0.95 | L | Th | Stage 3+ | | B+C |
| | | | | | | R | Th | Stage3+ | | B+C+P |
| **Mean** | | | | 28.4 | 0.9893 | | | | | |

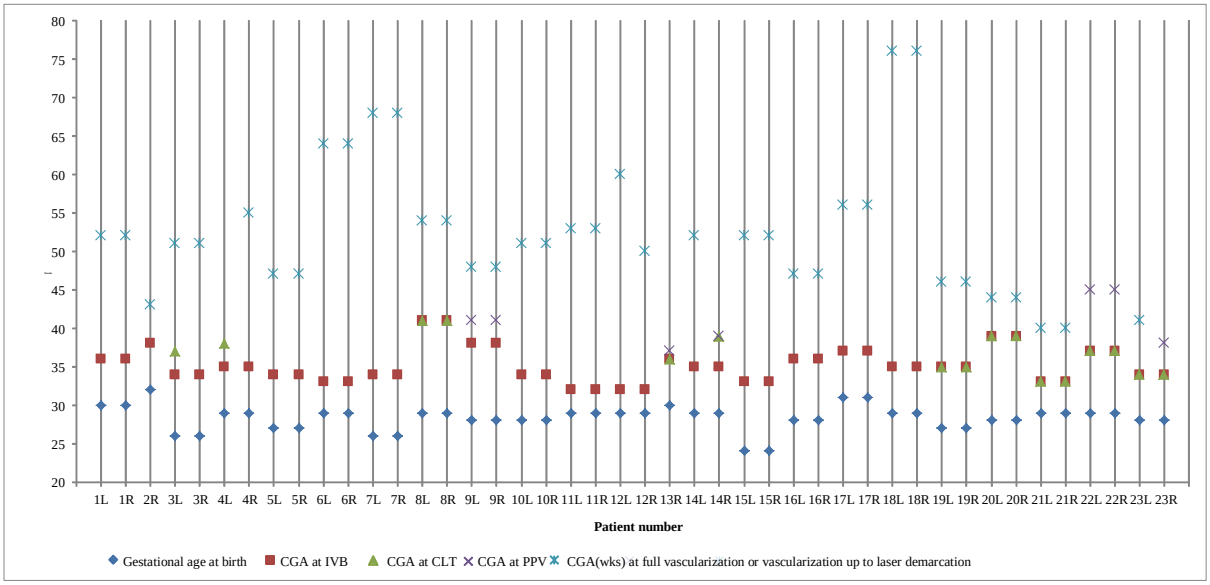
Eyes that progressed to retinal detachment

| | | |
|---|---|---|
| | Eyes that vascularized fully or up to laser demarcation | |
| | Only eye in the main analyses that had a permanent retinal detachment | |
| | GA:Gestational age in weeks, BW:Birth weight in kilogram, L:Left, R:Right | |
| | AP-ROP:Aggressive posterior ROP, Th:Threshold disease, Z1S3+:Stage 3with plus disease in zone 1, PP:Pre plus disease;N:Not noted in clinical notes | |
| | B:Intravitreal bevacizumab, C:Conventional Laser Treatment, P:Pars plana vitrectomy | |

# Outcome and intervention summary

| Patient nr | Avastin+CGA | Laser+CGA | PPV+CGA | Regression | Progression | Period between injection and vasc | CGA(wks) at full vascularization | Description of outcome |
|---|---|---|---|---|---|---|---|---|
| 1 | 36 | | | ✓ | | 16 | 52 | |
| | 36 | | | ✓ | | 16 | 52 | Some traction or dragging temporal,Gliosis at 3 o clock |
| 2 | 38 | | | ✓ | | 5 | 43 | |
| 3 | 34 | 37 | | ✓ | | 17 | 51 | |
| | 34 | | | ✓ | | 17 | 51 | |
| 4 | 35 | 38 | Father refused | | ✓ | | | Flat retina,some macular dragging.Parents refused PPV for |
| | 35 | | | ✓ | | 20 | 55 | |
| 5 | 34 | | | ✓ | | 13 | 47 | |
| | 34 | | | ✓ | | 13 | 47 | |
| 6 | 33 | | | ✓ | | 31 | 64 | |
| | 33 | | | ✓ | | 31 | 64 | |
| 7 | 34 | | | ✓ | | 34 | 68 | |
| | 34 | | | ✓ | | 34 | 68 | |
| 8 | 41 | 41 | | ✓ | | 13 | 54 | Vasc up to laser scars |
| | 41 | 41 | | ✓ | | 13 | 54 | Vasc up to laser scars |
| 9 | 38 | | 41 | | ✓ | | 48 | Flat retina with nasal gliosis post PPV for nasal S4a |
| | 38 | | 41 | | ✓ | | 48 | Flat retina with nasal gliosis post PPV for nasal S4a |
| 10 | 34 | | | ✓ | | 17 | 51 | |
| | 34 | | | ✓ | | 17 | 51 | |
| 11 | 32 | | | ✓ | | 21 | 53 | High myopia |
| | 32 | | | ✓ | | 21 | 53 | High myopia |
| 12 | 32 | | | ✓ | | 28 | 60 | |
| | 32 | | | ✓ | | 18 | 50 | |
| 13 | 36 | 36 | 37 | | ✓ | | | Funnel detachment |
| 14 | 35 | | | ✓ | | 17 | 52 | |
| | 35 | 39 | 39 | | ✓ | | | Flat retina with nasal gliosis post PPV for S4B |
| 15 | 33 | | | ✓ | | 19 | 52 | |
| | 33 | | | ✓ | | 19 | 52 | |
| 16 | 36 | | | ✓ | | 11 | 47 | |
| | 36 | | | ✓ | | 11 | 47 | |
| 17 | 37 | | | ✓ | | 19 | 56 | |
| | 37 | | | ✓ | | 19 | 56 | |
| 18 | 35 | | | ✓ | | 41 | 76 | |
| | 35 | | | ✓ | | 41 | 76 | |
| 19 | 35 | 35 | | ✓ | | 11 | 46 | Myopia |
| | 35 | 35 | | ✓ | | 11 | 46 | Myopia |
| 20 | 39 | 39 | | ✓ | | 5 | 44 | High myopia |
| | 39 | 39 | | ✓ | | 5 | 44 | High myopia |
| 21 | 33 | 33 | | ✓ | | 7 | 40 | High myopia |
| | 33 | 33 | | ✓ | | 7 | 40 | High myopia |
| 22 | 37 | 37 | 45 | | ✓ | | | High myopia.Flat retina post PPV for S4a |
| | 37 | 37 | 45 | | ✓ | | | High myopia.Flat retina with nasal gliosis post PPV for S4 |
| 23 | 34 | 34 | | ✓ | | 8 | 41 | |
| | 34 | 34 | 38 | | ✓ | | | Flat retina.Nasal and superotemporal gliosis post PPV for S |
| **Mean** | **35.18181818** | **36.75** | **40.85714286** | | | | **52.60526316** | |
| | | **PRP (laser)** | **PPV** | **Regressed** | **Progr** | **e between Avastin a** | **Vasc** | |
| | 44 eyes | 16 | 7 eyes | 36 eyes | 8 eyes | 17.94444444 | 38 pts | |
| | | | | | | | 86.36% | |
| | | | | | | | | |
| | | | | | | Mean of 55 weeks if laser disregarded | | |

## Outcome timeline




## Period in weeks between injection and vascularization