P.I.R.A.T.E. Study

Palmerston North Interventional Rapid Avastin Treat & Extend

Study Protocol 2022

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Investigator	**Vidit Singh** – *Ophthalmology Non-Training Registrar*		**Duration**	12 months (initial trial) 24 months (total duration)
Supervising Consultant	**John Ah-Chan** – *Consultant Ophthalmologist (FRANZCO)*		**Principal Research Location**	Palmerston North Hospital Mid-Central District Health Board, 50 Ruahine Street, Roslyn, Palmerston North, 4442, New Zealand

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1. Introduction

Background

Age-related macular degeneration (AMD) is the primary cause of blindness of individuals over the age of 50 years in New Zealand.[1] It is a lifelong chronic ocular condition requiring monitoring and treatment to prevent progression and irreversible visual loss. The prevalence of AMD is projected to increase by 20-40% over the next 10 years as a direct result of New Zealand's aging population.[1] The development of anti-Vascular Endothelial Growth Factor (anti-VEFG) medication has revolutionized the treatment of neovascular ("wet") age-related macular degeneration (nAMD) improving the visual prognosis of patients. This however has come at a cost, with the increasing provision of care becoming a major burden for all ophthalmology services.

Current Practice

With the current standardised treat and extend protocol (TAE), nAMD patients receive a loading dose of 3 Bevacizumab (Avastin) injections 4 weeks apart. The injection interval is then adjusted according to the level of disease activity. Patients with stable disease are extended by 2-week increments. For example; a patient receiving an Avastin injection every 4 weeks with stable disease activity would be subsequently extended to a 6-week injection interval. This would then be reassessed at the end of the 6-week treatment period to determine if it can be extended further to 8 weeks or requires to be reduced back to 4 weeks based on their disease activity (fluid-free status). Increment adjustments therefore only occurring at 2-week intervals.

Injection frequency not only affects patients' treatment burden but also leads to increasing demand on all aspects of ophthalmology service provision including; nurse-led injectors, macular review / hybrid clinic nurses, ophthalmology registrars and overseeing ophthalmologists. There are further constraints on physical space to perform injections and additional administrational work that accompanies intravitreal injection scheduling. Current practicing standards are unlikely to meet the projected increasing demand of nAMD patients expected over the next 10 years and therefore new innovative changes are required to current service provision.

Evidence in Support of Rapid Treat and Extend

Seeking ways to minimise the frequency of intravitreal injections has been researched extensively, aiming to increase injection capacity without compromising the patient's visual outcomes and the quality of care provided. A recent randomized controlled trial; ALTAIR, demonstrated that 4-week incremental treatment adjustments can be equally safe and effective in low-risk nAMD patients.[2] In the ALTAIR study, patients who underwent 4-week adjustments had similar 2-year visual outcomes when compared to those who underwent 2-week adjustments with fewer clinic visits and fewer total injections recieved.[2] However, this study was performed in a Japanese population and used Aflibercept (Eylea) rather than Bevacizumab (Avastin) which is the first-line anti-VEGF treatment for nAMD in New Zealand. The exceptional COVID-19 situation and pandemic lockdown has compounded the strain on medical retinal and injection clinics. This has led to unplanned treatment delays in some of our nAMD patients. Coincidentally, we have noticed that many patients with low-risk nAMD features were not adversely affected by delays in their treatment interval. This suggests that similar visual outcomes are possible as described in the ALTAIR study, but would require further research evidence to substantiate these observations.

Research Proposal (PIRATE Study)

In the Palmerston North Interventional Rapid Avastin Treat & Extend (PIRATE) study we propose to investigate a modified treat and extend protocol. In the modified protocol, treatment adjustments would be in 4-week increments in patients with a low-risk nAMD. As an additional safety feature, any patient who require interval shortening or experience any adverse event from rapid treatment extension will have their interval immediately shortened by 4 weeks, with subsequent extension as per the current standard 2-week protocol. Each eligible patient will be informed of participation in the trial and may further opt-out of 4-week adjustments at any point if they so choose. Through this trial we hope to provide evidence to support rapid

treatment extension of nAMD as a safe, efficient and practical method to adapt to our aging population and associated ophthalmic service constraints.

References:
1. National Health Committee. Age-related macular degeneration. Wellington, New Zealand: National Health Committee, 2015. Available from: http://nhc.health.govt.nz/
2. Ohji M, Okada AA, Takahashi K, Kobayashi M, Terano Y. Two different treat and extend dosing regimens of intravitreal aflibercept for wAMD in Japanese patients: 96 Week results of the ALTAIR study. Presentation at the 18th European Society of Retina Specialists (EURETINA) Congress; Vienna, Austria; 2018

2. Research Aim

1. Assess the safety and efficacy of Avastin treatment extension at 4-week intervals in patients with low-risk neovascular Age-Related Macular Degeneration.

3. Study Design

The PIRATE study will be a monocentric, prospective, interventional, randomized controlled trial conducted in Palmerston North Hospital Ophthalmology Department. It will be open-label and non-blinded. The initial trial will run for 12 months duration. Data will be audited and assessed with appropriate adjustments made for the second trial period spanning up to 24 months (assuming no significant adverse outcomes are found after 12 months).

Once appropriate approval has been obtained nvAMD patients will be recruited into the study. The following criteria will be applied for participant inclusion or exclusion;

Inclusion criteria:

- Patients ≥50 years of age
- Low-risk nvAMD characteristics (see risk-stratification below) with likely subfoveal or juxtafoveal choroidal neovascular membrane (CNVM). These being diagnosed clinically, confirmed by investigator (ophthalmology registrar or ophthalmologist)
- Deemed appropriate for Avastin therapy by investigator
- Best corrected visual acuity (BCVA) between 6/12 - 6/180 at first visit in study eye
- If both eyes affected then the eye with the worse BCVA will be included in the trial as the study eye
- Participants must be willing and able to provide independent informed consent

Exclusion criteria:

- Prior treatment of the study eye with intraocular anti-VEGF agents, verteporfin photodynamic therapy, other laser treatment, intraocular corticosteroids, surgical procedures (except cataract surgery ≥30 days prior to screening)
- Systemic use of anti-VEGF agents within 3 months prior to the study entry period
- Active or suspected infection in or surrounding the study eye
- Peripapillary CNVM
- Active severe intraocular inflammation in the study eye
- Intraocular pressure ≥28mmHg in study eye
- Ocular condition that might impact vision and confound study outcomes in the study eye (by the discretion of ophthalmology registrar or ophthalmologist)
- History of Avastin allergy or related intravitreal administration agents (e.g. povidone iodine, lidocaine, gutt. Iopidine, gutt. Chloramphenicol)

- Women who are pregnant, suspected to be pregnant or lactating
- Previous or concomitant participation in another clinical study with investigational medicinal product(s) within last 3 months
- Individuals who lack decision-making capacity who are not able to provide independent informed consent for the trial
- Any other patient deemed ineligible by investigator (ophthalmology registrar or ophthalmologist)

Participant Selection and Treatment allocation:

Participants may be considered for inclusion if they meet the above "inclusion criteria". Eligible patients which consent to inclusion into the trial will be recruited. Only low-risk nvAMD participants will be enrolled into the PIRATE trial (please see inclusion criteria). High risk nvAMD will not receive rapid Avastin treatment and extension, but rather continue with the standard treatment protocol. Low-risk nvAMD participants will subsequently be randomized to two treatment arms for comparison; those receiving 2-weekly increment extension (control group) and those 4-weekly extension (treatment group). Block randomization (block size of 4) will be utilized to ensure equal sample sizes and balanced base-line characteristics between groups.

Targeted Sample Size

The PIRATE study will include a target sample size of 100 participants. 50 are expected to be recruited during the initial study period. The study duration has been extended to now run for 12 months (initial trial period) and 24 months (total duration). According to Singh et al. (Intravitreal therapy in neovascular AMD: adapting to increasing demand and changing times) there were approximately 80 new nvAMD patients seen in MidCentral DHB in 2022, with a 20-30% increased annual incidence from 2019 – 2021. With these statistical figures considered the projected targeted size is practical and achievable.

No historical data will be used in the PIRATE study with respect to retrospective controls. The study will recruit in a prospective manner.

Therapeutics:

All individuals will be provided the same anti-VEGF treatment; 0.05mL Bevacizumab (Avastin) 3.75mg/0.15mL. This will be administered into the vitreous cavity in the standard method by either nurse injectors or ophthalmology registrars/ophthalmologists.

Patient Risk-Stratification

Participants with be stratified based on their nAMD characteristics. High-risk participants will be deemed anyone who meets one or more of the following criteria:

1. Monocular patients (i.e. only have a single good-seeing eye)
2. Macular haemorrhage (≥1DD) clinically or on fundus photo
3. History of previous of large macular haemorrhage
4. Subretinal fluids (SRF) > 200 microns
5. Recent reduction of injection frequency for any reason (*i.e. if shortened by 4 weeks, then further extensions will be at 2 week intervals or 'usual treatment' as in control group)*

High-risk participants will NOT be included in the PIRATE study cohort. They will continue with the current standard anti-VEGF therapy

Low-risk participants will be deemed anyone who meets the inclusion criteria WITHOUT having any of the high-risk criteria outlined. Low-risk participants will be grouped into the PIRATE study cohort and randomized into treatment (4-week adjustments) and control (2-week adjustments) groups using block randomization. Sealed envelope[3] will be used as the block randomization software platform.

References:
3. Sealed Envelope Ltd. 2021. Create a blocked randomisation list. [Online] Available from: https://www.sealedenvelope.com/simple-randomiser/v1/lists [Accessed 18 Jul 2022].

4. Outcome Measures

Primary outcome measure

1. BCVA at end of study period

Secondary outcomes measures:

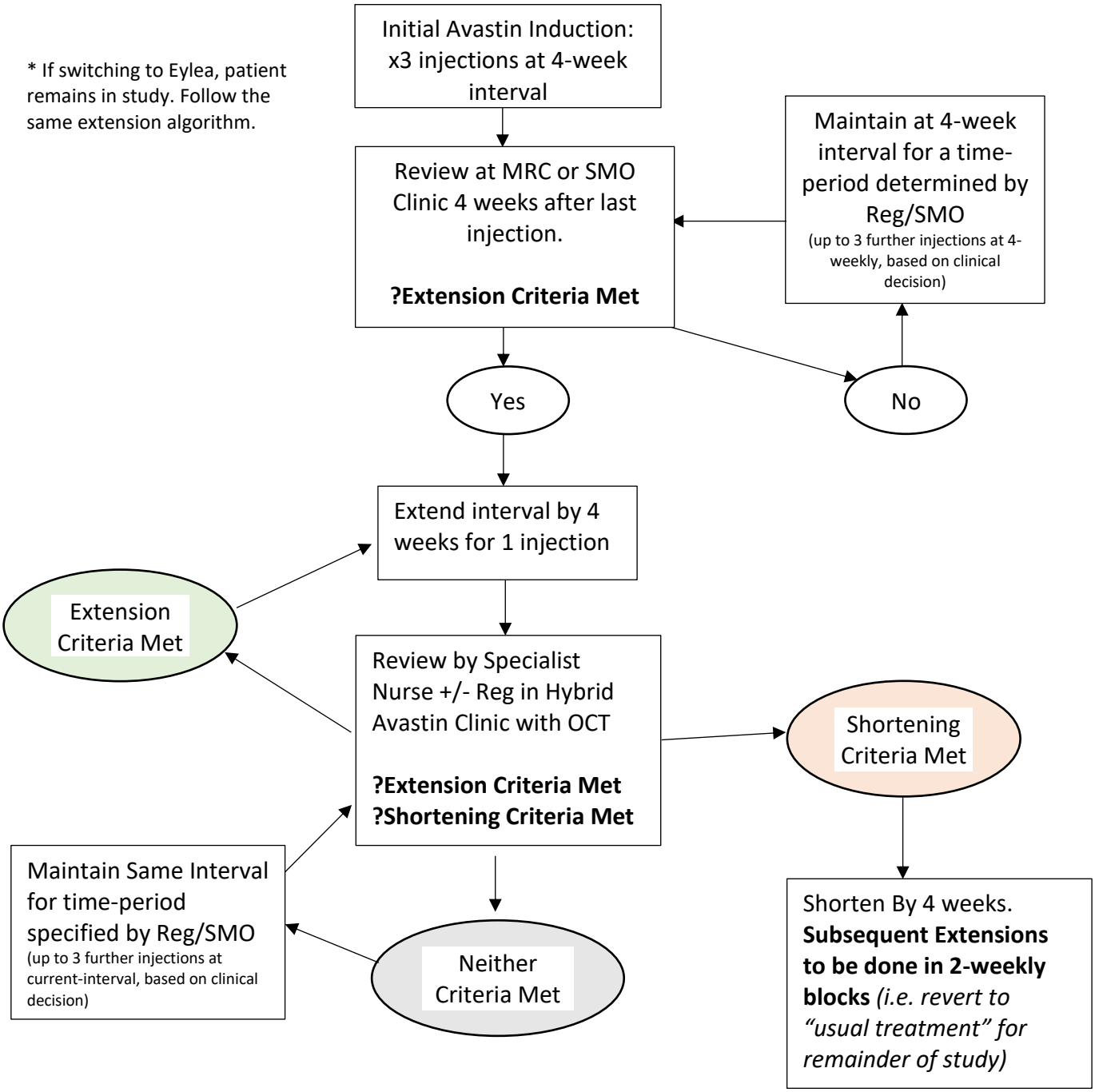
2. Central macular thickness
3. Number of adverse injection-related events
4. Whether treatment interval had to be shortened
5. Number of large macular haemorrhages
6. Total number of injections
7. Total number of AMD-related appointments

5. Methodology

Injection clinics and macular review clinics are already established and in operation in Palmerston North Ophthalmology. Upon approval, current medical and nursing staff will be briefed about the study protocol. It will be implemented in the following manner, outlined below:

Steps to follow for each eligible participant:

1. Discuss case with an ophthalmology registrar to confirm eligibility and inclusion criteria (or an SMO who has been briefed on the study protocol)
2. Consent the patient with the participant information sheet and consent form
3. Randomly allocate participant into treatment group or control group by block randomization and allocate research ID code (to be completed by principal investigator)
4. Follow the treatment algorithm below **IF THE PATIENT IS IN THE <u>TREATMENT GROUP</u>**
5. Researchers to record data on REDCap (principal investigator to be informed of each treatment event)



Criteria for Interval **Shortening**	If any of the following are met: ○ New or persistent fluid with unchanged or increased fluid on OCT ○ Loss of >5 EDTRs letters visual acuity ○ Increase in CRT of >100 microns (in central 1mm region) compared to the lowest value measured on OCT ○ New neovascularisation as determined by investigator ○ New macular Haemorrhage
Criteria for Interval **Extension**	○ No criteria for shortening met ○ No intraretinal/subretinal fluid present on OCT
Criteria for **Maintaining Current Interval**	○ No shortening or extension criteria met (i.e. stable and residual fluid has reduced but NOT completely resolved)

6. Health and Safety

Human tissue collection

No human tissue will be collected as part of the PIRATE study.

7. Data Management Plan (DMP)

- Data management considerations according to Chapter 12 of National Ethics Advisory Committee (NEAC) have been addressed. The 44 relevant sub-sections (12.1 – 12.44) have been considered and addressed under the following headings;

Māori data (12.1, 12.2)

- All participants will be collaboratively involved in decisions regarding the collection and use of their data within the PIRATE study including Māori and Pacifica.
- Health governance accessibility within the PIRATE study will comply with the Māori Data Sovereignty principles (Te Mana Raraunga). We recognize that Māori have a right to exercise control over their data and self-determination with respect to what data is collated and used. We respect that data has whakapapa/genealogy association.
- The collection, use and interpretation of data will ensure to uphold the dignity of Māori communities and individuals. Informed consent shall underpin all collection of data. Māori data will be stored within the same REDCap data capture platform as for all participants.

Data identifiability (12.3, 12.4, 12.4, 12.6, 12.7)

- No direct identifiers will be recorded in REDCap, which is the agreed upon data capture platform for the PIRATE study. De-identified data may be included such as; age, gender, ethnicity etc. An encrypted research ID code will be used to associated participants' NHI.
- Re-identifying data is not expected to occur during analysis. The associated risks of re-identification (physical, social, economic, psychologic, legal and interpretation harm) have been assessed and risk-mitigation considered by the way of only analyzing de-identified data.
- The benefits of data collection through the PIRATE study is expected to far exceed the potential risks as outlined in NEAC standards. Only data required to assess the safety, efficacy and impact of rapid treatment and extension of Avastin therapy in low-risk nvAMD participants (i.e. the research aim) will be collected.

Privacy and confidentiality (12.8, 12.9, 12.10)

- Researchers involved in the PIRATE study will record and respect any restrictions participants have or place on the use of their health data. Only authorized researchers involved in the PIRATE study will handle participant's data.
- All health data will be protected with confidentiality except in exceptional circumstances as outlined by the NEAC standard guidelines (e.g. disclosures required by law, on grounds of serious and imminent threat to public health, public safety or the life or health of the individual).
- With respect to "unauthorized disclosure plans", the confidentiality and privacy policy (DOC CODE: HRC6) which governs all health-related data collected within MidCentral DHB will be adhered to in the PIRATE study. This policy is compliant with the Health Information Governance Guidelines, Privacy Act 1993 and Health Information Privacy Code 1994.

Storage, governance and management of data (12.11, 12.12, 12.13)

- Data will be recorded digitally on data capture platform; REDCap, which is considered a highly reputable, secure global platform endorsed by universities, teaching hospitals and research institutions alike. This was also the agreed upon data management platform recommended by the HDEC committee.
- Access to the database will be password protected with only authorized researchers being granted access under the discretion of the principal investigator and supervising clinician.
- As mentioned previously; no identifiable data will be recorded within REDCap.
- A master log of the participant's research ID code will be maintained within a locked, secure location accessible only to the principal investigator and supervising clinician.

Organisational and researcher data guardianship (12.14, 12.15)

- The sole purpose of data collection within the PIRATE study is to assess the safety and efficacy of rapid treatment and extension of Avastin therapy in low-risk nvAMD. The study is monocentric without secondary site involvement or data sharing.
- There is no funding or grants being received for the PIRATE study either by the Ministry of Health / New Zealand Government, local district health-board or private entities. There is no pharmaceutical sponsorship.
- Data collection, handling and analysis is solely voluntary by researchers without financial incentive. Each researcher is bound by the data guardianship of MidCentral District Health Board (MDHB). Procedures dealing with breaches of privacy and confidentiality will be handled in accordance with the MDHB confidentiality and privacy policy (DOC CODE: HRC6).

Sending and/or storing data overseas (12.16, 12.17)

- No physical or digital data will be stored overseas. The PIRATE study is a monocentric, hospital-based study conducted within Palmerston North Hospital. Consent is therefore not required to be sought for overseas data storage.

Directly-collected new data (12.18, 12.19, 12.20, 12.21, 12.22, 12.23, 12.24, 12.25)

- Data collection during the PIRATE study will be in accordance with Health Information Privacy Code 2020. Researches will obtain the participants consent before the recording of their health-related data with attention placed on their individual preferences and cultural requests.
- As data collected is solely related to a participant's ocular disease and relative treatment, "unreasonably intrusive information" will not be formally collected (12.20a – i.e. relating to a person's sexual preferences, HIV status, sexually-transmitted disease history, mental-health status, life expectancy or addiction).
- All data will be collected within Palmerston North Hospital, there is no privacy concerns relating to the physical research environment (12.20b – i.e. prisons, rest-homes, schools, hospice etc.)
- All researchers involved in the PIRATE study have the appropriate specialised knowledge within the scientific field to accurately collect participant data. All clinical decision-making will be overseen by a consultant ophthalmologist.
- Only data necessary for the specified research aim of the study will be collected.

Determining sensitivity, level of consultation and level of data management (12.26, 12.27, 12.28, 12.29, 12.30)

- The appropriate hui process has already been followed and completed with the MidCentral District Health Board research committee.
- There are no other contributing stakeholders, Māori community members which will be collecting and/or analyzing health-related data within the PIRATE study.

- Māori and Pacifica Health considerations, including Kaupapa methodology, have already been addressed in the protocol without concern raised by the HDEC committee (please see section 10 of the protocol)
- As data will be collected prospectively no waiver of consent is required for secondary re-use of identifiable health data.

Data-Linking and Databanks (12.31, 12.32, 12.33, 12.34, 12.35, 12.36, 12.37, 12.38, 12.39, 12.40, 12.41, 12.42, 12.43, 12.44)

- The PRIATE study is monocentric with a single collated database. New health-related data will be collected prospectively for research purposes to address the primary research aim.
- No data-linking will occur internally or externally to the study.
- No data-linking has been proposed.
- No third-party data-linking has been proposed.
- The PIRATE study is a regional, monocentric study without association with national/international public health registries. The subsequent privacy issues related to these are therefore not applicable.
- The SharePoint database already in operation within Palmerston North will run independently to the PIRATE study.
- Complete separation of clinical data-collection from research data-collection has been established in the PIRATE study, as requested by the HDEC committee.

Other DMP considerations:

- As recommended by the HDEC committee; participant consent forms will be secured separately from their patient record. These will be managed and stored in a locked location only accessible to the principal investigator and clinical supervisor as recommended by the committee. Under the advice of the committee, no research data will be maintained in the participant's clinical record.

8. Māori & Pacifica Health

Māori & Pacifica Recognition, Relevance and Benefit

Māori and Pacific people make up 13.1% of the entire 45–85 year age demographic of New Zealand.[3] The prevalence of AMD amongst Māori and Pacifica is under-reported, likely due to low utilisation of health services, but approximated to be less than 3%.[3] In contrast Māori and Pacifica are over-represented in rates of vision loss secondary to diabetic retinopathy; 2.28 times that of non-Māori within the same age demographic.[4] Due to the relatively rare nature of AMD amongst Māori, the direct impact of the PIRATE study is likely to be lower than other ethnic populations. The indirect impact however will be significant, as it is expected to increase treatment capacity for Māori and Pacifica who are disproportionally affected by other ocular disease. As the PIRATE study allows for fewer nAMD-related Avastin injections, more time, resources and clinic space will be made available for treatment of diabetic eye disease of which Māori and Pacifica are disproportionally more affected. It will allow Avastin injections be provided in a timelier manner to prevent worsening of visual outcomes. The PIRATE study will further allow more clinician time to educate patients, including Māori and Pacifica individuals, which is anticipated to have a positive effect on treatment compliance and long-term health outcomes.

Kaupapa Māori Methodology

There is no racial or cultural discrimination in the PRIATE study. Participation is welcomed from all ethnic backgrounds, including Māori and Pacifica individuals which meet the pre-determined inclusion criteria. In the PIRATE study we will acknowledge the Kaupapa Maori principles as initially described be Graham Hingangaroa Smith (1990).[5]

1. **Tino Rangatiratanga:**
   All participants meeting the predetermined inclusion criteria will be offered participation into the PIRATE study. It will not be forced on anyone, and those which decline will receive uninterrupted anti-VEGF treatment. Those that decline will receive Avastin injections at 2-week increment adjustments as per the current protocol. Autonomy and self-determination will be upheld for everyone, including Māori and Pacifica participants.

2. **Taonga Tuku Iho:**
   The PIRATE study recognises the centrality and legitimacy of Te Reo Māori and the Māori "ways of knowing and doing."[5] The primary language of the study protocol, participant information sheet and consent will be in English for scientific accuracy and effective communication. The Ihi© mobile app by ProCare can be used at the participant's request to allow for synchronised narration in Te Reo Māori.

3. **Kia piki ake I ngā raruraru o te kainga:**
   Patient recruitment will be non-discriminatory to ethnicity, race and socioeconomic background. Participant inclusion will be based solely on the inclusion/exclusion criteria outlined with risk-stratification solely on nAMD disease characteristics. Māori and Pacifica individuals of all socio-economic backgrounds are welcomed and encouraged to participate. The benefits of the PIRATE study, as stated before, are projected to increase the treatment capacity available to Māori and Pacifica for other ocular disease (e.g. diabetic eye disease).

4. **Whānau:**
   The PIRATE study recognises the importance of Whānau and the relationship Māori have to one another. With the permission of the patient involved, family/whānau can be included in the shared decision-making and consenting process.

5. **Kaupapa:**
   We recognise the importance of kaupapa and the collective vision, aspiration and purpose of Māori communities. The health inequalities faced by Māori have been well documented.The benefits of the PIRATE study are projected to increase the treatment capacity available to Māori and Pacifica for diabetic-related eye disease by reducing the nAMD-related injection frequency. This aims to meet the health disparity currently facing Māori and Pacifica people.

Cultural data-handing issues

No apparent issues have been identified, or are anticipated to impact data sovereignty affecting Māori participation. No additional data will be stored for this study beyond that which is already collated on a daily bases from AMD patients receiving anti-VEGF injections.

Tapu:

We recognise the cultural importance of tapu and the sacred and spiritual restriction placed on the head and body within the Maori worldview. As the PIRATE study will involve intravitreal injections, it will involve touching the head of the participant in order to administer the necessary treatment. We acknowledge that the head is the 'most tapu' of the body and one's degree of tapu may be further elevated in times of sickness or disease. The greatest degree of sensitivity and cultural-awareness will be implemented when administering intraocular treatments. Instruments, medications and sterilisation equipment will be passed around rather than directly above the person's head (wherever reasonably possible) to ensure not to dishonour their tapu. An open dialogue is welcomed amongst all participants regarding their individualistic view on tapu. Every effort will be made to respect their wishes within what is reasonably possible, not to compromise current health practicing standards. These judgements will be made in collaboration between patient and investigator.

Taonga/Valuables/Possessions

We recognise the importance of possessions being treasured and assigned spiritual value. Participants within the study will be required to remove their individual spectacles, contact lenses or head coverings (if obstructing their orbit/eye) in order to access, examine and treat their eye disease. We will ensure to do so in a sensitive and collaborative manner. Where possible we will provide the individual the option of removing their body taonga himself or herself. Other items of clothing, including greenstone necklaces will be allowed to be kept on the person as long as they do not impede the sterile field. In cases where sterility may be compromised, for the health and safety of the patient, the taonga will be requested to be removed temporary until after the procedure is completed.

Whakamā

Individuals may present to the eye clinic in a vulnerable state particularly in the presence of illness and/or ocular disease. This may affect their quality of life and world-view. Interaction of Māori with non-Māori within a hospital setting, particularly when vulnerable, may lead to self-abasement and the feeling of self-doubt and inferiority. Care will be taken to construct patient encounters in a collaborative manner, ensuring to be non-judgemental, supportive and culturally-aware. This is already standard practice within the eye clinic, and will continue to be implemented for all components of PIRATE study.

Genetics / Whakapapa Consideration

There is no genetic research incorporated within the PIRATE study. No genetic engineering, DNA sampling or manipulation will be carried out. There are therefore no foreseeable cultural issues regarding sensitivity to Maori Whakapapa, or inducing indigenous diversity.

Maori Consultation

The Hui process has been followed and completed with the MidCentral District Health Board research committee. This was coordinated by corresponding research officer Annette Carse (annette.carse@midcentraldhb.govt.nz). Further documentation can be supplied on request.

Contribution to reducing Maori and Pacific people health inequality

The PIRATE study will incorporate the principles of Maori participation, partnership and protection. It is anticipated that a greater service provision to Maori, particular with respect to Diabetic Eye Disease. This will act to address the health inequality that currently exists. There will be equal access to all ethnicities to participate in the PIRATE trial with non-discriminatory inclusion criteria. The PIRATE trial will contribute to the medical retinal treatment field of which Māori and Pacific people will benefit both directly and indirectly. Results of the study will be made available and freely shared with all participants.

References:

3. Worsley D, Worsley A. Prevalence predictions for age-related macular degeneration in New Zealand have implications for provision of healthcare services. NZMJ. 2015;128:1409.
4. Access Economics. Clear focus – the economic impact of vision loss in New Zealand. Reported by Access Economics for Vision 2020 Australia in support of vision 2020 New Zealand Trust. 2010.
5. Smith, G. H. Kaupapa Maori theory: theorizing indigenous transformation of education and schooling. University of Auckland & Te Whare Wananga o Awanuiarangi: tribal-university. Auckland, New Zealand. 2003.
6. Sachdev PS. Whakama: culturally determined behaviour in the New Zealand Maori. Psychol Med. 1990;20(2):433-44.

9. Ethical Considerations

Financials and Conflicts of Interest

There are no conflicts of interest to disclose by any of the investigators or involved staff. No additional funding has been acquired for this study. Current infrastructure will be utilized including established injection clinics, macular review / hybrid review and medical retina specialist clinics.

Only patients newly diagnosed with nAMD will be enrolled in the study (rather than patients who are long-term patients of the department). These patients will be recruited into the study in a streamlined process with the ophthalmology registrar. Non-health providers, not directly involved in their clinical care, will be available to explain the study protocol to all participants and answer any questions they may have.

The patient and their family actually have 3 months to choose whether to enrol in the study, as the first alteration in treatment between the two groups does not occur until after the third monthly injection. This reduces opportunity for coercion or undue influence in enrolling in the study.

Appendix:

Checklist for Recruiting New Patients into the PIRATE Study

- Anti-VEGF Naive and listed for *or currently undergoing* Series of 3 Avastins 4-weekly
- Patient > 50 years old
- AMD with likely Sub-Foveal or Juxtafoveal CNVM (not Peripapillary CNVMs)
- "Low Risk AMD"
    - No Large Macular Haemorrhage on Fundus Photo/Examination ("specks" of haemorrhage are fine)
    - SRF < 200 microns on OCT
    - Not an "Only-Eye" patient
    - No previous history of large macular haemorrhage in same eye
- BCVA between 6/12 and 6/180 at time of recruiting
- If both eyes affected then eye with worse BCVA is recruited
- No previous laser or IVT
- No previous ocular surgery (other than cataracts > 30 days prior)
- No systemic anti-VEGF use in past 3 months
- No active/suspected ocular/periocular infection
- No recent/active severe ocular inflammation (e.g. uveitis or scleritis)
- No IOPs >28 at time of recruiting
- Other significant sight-limiting condition (e.g. dense cataract, corneal scarring, macular hole, significant DR)
- Not a close relative/friend of any eye clinic staff member
- Not involved in another clinical study
- Both willing and able to provide independent informed consent

PIRATE Study

Palmerston North Interventional Rapid Avastin Treat & Extend

MIDCENTRAL DISTRICT HEALTH BOARD
Te Pae Hauora o Ruahine o Tararua

Participant Information Sheet

You are invited to take part in the Palmerston North Interventional Rapid Avastin Treat and Extend (PIRATE) study. Whether or not you take part is your choice. If you do not want to take part, you do not have to give a reason, and it will not affect the care you receive. You are free to decline to participate, or to withdraw at any practicable time.

This Participant Information Sheet will help you decide if you would like to take part. It sets out why we are doing the study, what your participation would involve, what the benefits and risks to you might be. We will go through this information with you and answer any questions you may have. If you agree to take part in this study, you will be asked to sign the Consent Form on the last page of this document. You will be given a copy of both the Participant Information Sheet and the Consent Form to keep. This document is 4 pages long, including the Consent Form. Please make sure you have read and understood all the pages.

What is the purpose of this study?

The PIRATE study is assessing if individuals with "wet" Age-related Macular Degeneration (AMD) can have their injection intervals extended more quickly (i.e. by 4-week increments rather than 2-week increments as demonstrated graphically below). The results of this study may allow fewer injections to be safely administered while still maintaining an individual's visual improvement. The evidence for this study proposal stems from the ALTAIR trial, a large Japanese study using a similar injection treatment; Aflibercept (Eylea). The PIRATE study is being conducted to see whether these findings apply to a New Zealand population with Bevacizumab (Avastin).

How is the study designed?

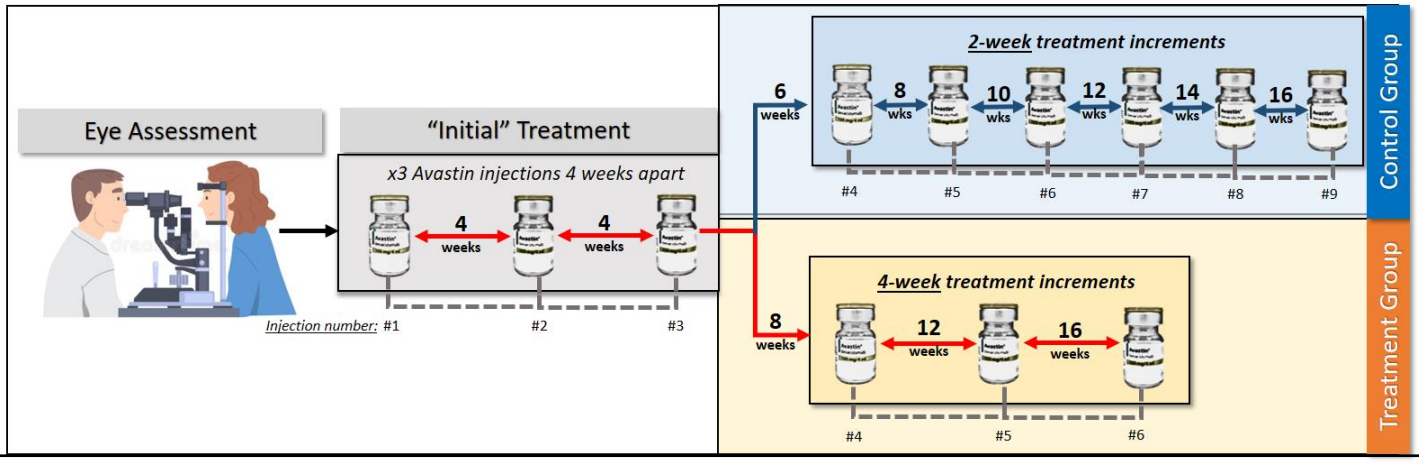
This study is conducted voluntarily by the ophthalmology staff of Palmerston North Hospital. Participants will be recruited, receive treatment and have all associated follow-up in Palmerston North Hospital Eye Clinic. No additional testing, follow-up or travel will be required by enrolment in the study. All research-data will be carried out during your scheduled clinic appointments. Approximately 100 participants will be recruited into the PIRATE study which is expected to run over a 2 year period.

Who can take part in the study?

This study is intended for individuals with "wet" AMD with low-risk features who are eligible for Avastin treatment. You have been provided this information sheet because you have been deem eligible to participate in the study. There is no additional medication or lifestyle restrictions required by participants outside your usual post-injection instructions (*as outlined on the general procedure consent form*).

What will my participation in the study involve?

Eligible individuals who consent to participation will be placed in one of two groups (treatment group and control group). Group allocation will be assigned randomly. After the initial injection series (x3 injections of Avastin at a 4-week interval), subsequent injection intervals will be extended by 4-weeks (treatment group) or 2-weeks (control group / standard protocol). No additional assessments or clinic visits are required outside these treatment periods (*summarised below*)



What are the risks of participating in the study?

The methods employed in this study mirror that of the ALTAIR study which has showed to be both safe and effective. There is a possibility that the "wet" changes within the macular do not improve during the treatment period resulting in similar or worse vision in the affected eye. You will be monitored closely and if this occurs you will be changed back to the standard treatment protocol with any further injection increments occurring at 2-week intervals. The mode of administration of Avastin and associated injection-related risks remain unchanged (*as outlined on the general procedure consent form*).

What are the benefits of participating in the study?

Participation is greatly valued as you are directly contributing to the advancement of knowledge which facilitates better evidence-based care for future patients. If selected within the treatment group of the study you will potentially receive less injections, fewer clinic appointments and theoretically fewer injection-related complications. If there is any indication that you may not be responding to the treatment (i.e. your "wet" AMD is not "drying out") then you will be returned to the standard treatment protocol.

What are the alternatives to taking part?

The alternative to not partaking in this study will be to receive treatment under the standard protocol.

Will any costs be reimbursed? Who is funding the study?

Participants will not incur any costs. Participants and researchers alike will not receive reimbursement for involvement within the PIRATE study. There is no funding received for this study either by the Ministry of Health / New Zealand Government, private entities, pharmaceutical companies or other third-party sponsors. All involvement within the PIRATE study is voluntary and unpaid.

What if something goes wrong?

If you were injured in this study, you would be eligible to apply for compensation from ACC just as you would be if you were injured in an accident at work or at home. This does not mean that your claim will automatically be accepted. You will have to lodge a claim with ACC, which may take some time to assess. If your claim is accepted, you will receive funding to assist in your recovery. If you have private health or life insurance, you may wish to check with your insurer that taking part in this study won't affect your cover.

What will happen to my information?

During this study researchers will record information about you and your study participation related to your injections and response to treatment. If needed, information from your hospital records may also be collected. You cannot take part in this study if you do not consent to the collection of this information. The results of the study may be published or presented, but not in a form that would reasonably be expected to identify you. Your national health identifier (NHI) number will be used to assign you a research ID code which will be used during the duration of the study. To make sure your personal information is kept confidential, information that identifies you will not be included in any report. Your identifiable information is held at Palmerston North Hospital during the study. After the study it is transferred to a secure archiving site and stored for at least 12 months then destroyed. Your coded information will be entered into electronic data capture platform; REDCap. Your coded information will only be used for the PIRATE study and not for any future research. All storage will comply with local and/or international data security guidelines. Although efforts will be made to protect your privacy, absolute confidentiality of your information cannot be guaranteed. Even with coded and anonymised information, there is no guarantee that you cannot be identified. You have the right to request access to your information held by the research team. You also have the right to request that any information you disagree with is corrected. You may access other study-specific information before the study is over, but this could result in you being withdrawn from the study to protect the study's scientific integrity. If you have any questions about the collection and use of information about you, you should ask the principal investigator (contact details below). You may withdraw your consent for the collection and use of your information at any time, by informing your Study Doctor. If you withdraw your consent, your study participation will end, and the study team will stop collecting information from you. Information from this study may lead to discoveries and inventions or the development of a commercial product. The rights to these will belong to the principal investigators of the PIRATE study. You and your family will not receive any financial benefits or

compensation, nor have any rights in any developments, inventions, or other discoveries that might come from this information. The use of technology is not a mandatory component of study participation.
Māori data sovereignty is about protecting information or knowledge that is about (or comes from) Māori people. We recognise the taonga of the data collected for this study. A hui process has been followed with the MidCentral District Health Board research committee around the collection, ownership and use of study data. We allow Māori organisations to access de-identified study data, for uses that may benefit Māori if deemed appropriate.

What happens if I don't want to participate in the study or change my mind?

Study participation is completely voluntary and will not affect your treatment if you chose to participate or not. You are able to withdrawal your consent at any time during the study. You are able to inform any of the researches of your wishes to withdraw. You will still receive treatment as directed by your doctor without any incurred cost. Participation will not prevent you from being eligible for Eylea injections if clinically indicated in the future.

Can I find out the results of the study?

Participants will be provided with a summary of study results, if requested. This is expected to be available within 12 months of completion of the study.

What are your rights?

- You have the right to request access to your information recorded by the research team. This can be requested at any time prior, during or after the study period.
- You may withdraw your consent for participation in the study at any time. If you wish for this to occur please discuss this with your study doctor. (*Please note that information collected up until your withdrawal from the study will continue to be used and included in the study. This is to protect the quality of the study).*
- You have the right to ask for more information or further clarification of any component of the study.
- You have the right to be treated with respect of your personal health views, religious belief and cultural practice.
- You are protected by the Code of Health and Disability Service Consumers' Rights which provide the following 10 rights; the right to be treated with respect, right to freedom of discrimination, coercion, harassment and exploitation. The right to dignity and independence. The right to be fully informed, effectively communicated and provided services of an appropriate standard. The right to make an informed choice, ask for support and the right to respect teaching/research. Finally, the right to complain without fear of repercussions of care. You can find out more about your rights online; https://www.hdc.org.nz/your-rights/the-code-and-your-rights/

Who has approved the study?

This study has been approved by an independent group of people called a Health and Disability Ethics Committee (HDEC), who check that studies meet established ethical standards. The Northern B Health and Disability Ethics Committee has approved this study. The scientific aspects of this study have been approved by the Standing Committee on Therapeutic Trials (SCOTT), which is part of Medsafe.

PIRATE Study

Palmerston North Interventional Rapid Avastin Treat & Extend

MIDCENTRAL DISTRICT HEALTH BOARD
Te Pae Hauora o Ruahine o Tararua

Principle Research Location:
Palmerston North Hospital, 50 Ruahine Street, Roslyn,
Palmerston North, 4442, New Zealand

Participant Information Sheet adapted from New Zealand Health and Disability Ethic Committees website;
https://ethics.health.govt.nz/guides-templates-and-forms/

Health and Disability Ethics Committees

ANZCTR Australian New Zealand Clinical Trials Registry

Contact Information:

If you have any questions, concerns or complaints about the study at any stage, you can contact:

Dr. Antoine Bonnet, PIRATE Study Principal Investigator
Phone: 06 3508615
Email: piratestudynz@gmail.com

If you want to talk to someone who isn't involved with the study, you can contact an independent health and disability advocate on:

Phone: 0800 555 050
Fax: 0800 2 SUPPORT (0800 2787 7678)
Email: advocacy@advocacy.org.nz
Website: https://www.advocacy.org.nz/

For Māori health support please contact:

Pae Ora Whānau Care Services
Office hours; Mon-Fri; 0830-1630.
Phone: 06 3508210
Fax: 06 3508158
Email: customer@midcentraldhb.govt.nz

You can also contact the health and disability ethics committee (HDEC) that approved this study on:

Phone: 0800 4 ETHIC
Email: hdecs@health.govt.nz

PIRATE Study

Palmerston North Interventional Rapid Avastin Treat & Extend

MIDCENTRAL DISTRICT HEALTH BOARD
Te Pae Hauora o Ruahine o Tararua

Patient Details
(BRADMA placed here)

Participant Consent Form

I, _____ (full name) hereby consent to participating in the Palmerston North Interventional Rapid Avastin Treat & Extend (PIRATE) Study. I have read and understood the participant information provided. By consenting, I acknowledge the following:

	YES	NO
I have been given sufficient time to consider whether to participate in this study.		
I have read, or have had read to me in my first language, and I understand the Participant Information Sheet.		
I have had the opportunity to use a representative, whanau/ family support or a friend to help me ask questions and understand the study.		
I am satisfied with the answers I have been given regarding the study and I have a copy of this consent form and information sheet.		
I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time without this affecting my medical care.		
I consent to the research staff collecting and processing my information, including information about my health.		
I understand that my participation in this study is confidential and that no material, which could identify me personally, will be used in any reports on this study.		
I know whom to contact if I have any questions about the study in general.		
I understand my responsibilities as a study participant.		
I agree to an approved auditor appointed by the New Zealand Health and Disability Ethics Committees, or any relevant regulatory authority or their approved representative reviewing my relevant medical records for the sole purpose of checking the accuracy of the information recorded for the study.		
I wish to receive a summary of the results from the study when completed.	Yes ☐	No ☐

Declaration by participant:

I hereby consent to take part in this study.

Participant's name: _____

Signature: _____ Date: _____

Declaration by member of research team:

I have given a verbal explanation of the research project to the participant, and have answered the participant's questions about it. I believe that the participant understands the study and has given informed consent to participate.

Researcher's name: _____

Signature: _____ Date: _____