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Original Article – Clinical Science

Intravitreal dexamethasone versus bevacizumab in Aboriginal and Torres Strait Islander patients with diabetic macular oedema: The OASIS Study (A randomised control trial)

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-Registration SITE: The Australian New Zealand Clinical Trials Registry

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ABSTRACT

Background: Frequent intravitreal anti-VEGF injections are impractical for many Aboriginal patients with diabetic macular oedema (DMO). The longer acting intravitreal dexamethasone implant (DEX-implant) is approved for DMO but has not been assessed in an Aboriginal population.

Methods: This was a prospective, multicentre, randomized, single-masked, non-inferiority clinical trial. Aboriginal adults from Western Australia with DMO were randomized to receive 3-monthly DEX-implant, or monthly intravitreal bevacizumab. The primary outcome was the change in best corrected visual acuity (BCVA) at 12 months.

Results: The final endpoint was analysed for 24 DEX-implant and 28 bevacizumab injection eyes. Mean BCVA improved by 4.0 letters (-0.08 LogMAR) in the DEX-implant group and worsened by 5.5 letters (0.11 LogMAR) in the bevacizumab group. Before adjusting for cataract surgery, the upper bound of the two-sided 90% CI for the DEX-implant was 3.5 letters (0.07 LogMAR), which met non-inferiority criteria. The BCVA of remote participants who received the DEX-implant improved by 5.5 letters (0.11 LogMAR), compared to an 18.5 letter (0.37 LogMAR) decline for bevacizumab (P=0.04). The incidence of steroid-induced ocular hypertension for the DEX-implant was 33.3%.

Conclusions: Before adjusting for the effect of cataract surgery, the DEX-implant was non-inferior to bevacizumab for treating DMO in Aboriginal participants. In remote participants, the DEX-implant surpassed non-inferiority to achieve superior outcomes to bevacizumab. The incidence of steroid-induced hypertension was comparable to that reported in non-Aboriginal populations. We provide guidelines for the judicious use of DEX-implant among Aboriginal people, and a framework for performing ophthalmic clinical trials in Aboriginal communities.

Keywords: Aboriginal Australians, Diabetes, Diabetic Macular Oedema, Dexamethasone Implant, Bevacizumab

1. INTRODUCTION

In Australia, diabetic retinopathy (DR) accounts for three times as much vision loss among Aboriginal and Torres Strait Islander (hereby referred to as 'Aboriginal') people, when compared with non-Aboriginal people.[1] Most of this vision loss is attributable to diabetic macular oedema (DMO), which is found in 7.6% and 4.9% of Aboriginal and non-Aboriginal people with diabetes mellitus (DM), respectively.[2] These findings among Aboriginal people are multifactorial, with causes that include an earlier onset of type 2 DM, a more aggressive phenotype of DR, lower rates of retinal screening, late diagnosis, poor glycaemic control, and barriers to accessing treatment.[3,4]

For ophthalmologists who work in Aboriginal Medical Services (AMS) and other outreach settings, intravitreal bevacizumab (Avastin; Genentech, South San Francisco, CA) is the most common agent of choice for the treatment of DMO, due to its easier procurement and comparable clinical outcomes to other anti-VEGF agents.[5] However, monthly injections are impractical for many Aboriginal patients due to geographical, cultural and other barriers.[6] For example, in the state of Western Australia, 59.9% of Aboriginal people live in remote communities, located up to 3,000 km from the capital city of Perth, contributing to a lower utilization of ophthalmic services.[7] Similar trends have been reported for Indigenous populations living in other developed countries, including Canada and the USA.[8,9] Consequently, an effective alternative to anti-VEGF injections is needed among Aboriginal and Indigenous patients with DMO in Australia and overseas.

The dexamethasone implant (DEX-implant; Ozurdex, Allergan Inc., Irvine, CA) has a longer duration of action than anti-VEGF agents, with the intravitreal concentration sustained for up to 6 months.[10] Clinically, this translates to less frequent injections than anti-VEGF therapy, with comparable efficacy in terms of best corrected visual acuity (BCVA) and central macular thickness (CMT).[11]

The side effects of the DEX-implant include cataract formation, and steroid induced ocular hypertension (OHT) and glaucoma,[11] requiring timely follow-up and management. The incidence of steroid-induced OHT, however, has never been studied in an Aboriginal population. Moreover, there has never been an ophthalmic

randomized controlled trial (RCT) for Aboriginal patients in Australia, nor any Indigenous population globally, due to the presence of the historical barriers preventing this form of research.[12]

In this study, we sought to address the gaps in evidence described above, by performing a pragmatic RCT for Aboriginal participants with DMO in Western Australia.

2. METHODS

2.1 Study Design

The OASIS study was a prospective, randomized, active-controlled, non-inferiority trial of DEX-implant versus bevacizumab for Aboriginal adults with DMO in metropolitan and remote Western Australia (anzctr.org.au identifier ACTRN12618000202268, clinicaltrials.gov identifier NCT04619303, full protocol available at https://www.lei.org.au/research/clinical-trials/). The Western Australia Aboriginal Health Ethics Committee approved the trial protocol, which adhered to the tenants of the Declaration of Helsinki. A framework of enabling factors was incorporated into the study design, including formal executive endorsement from all participating AMS providers, to facilitate research in Aboriginal communities (Table 1).

Table 1: Framework of enabling factors in the study design

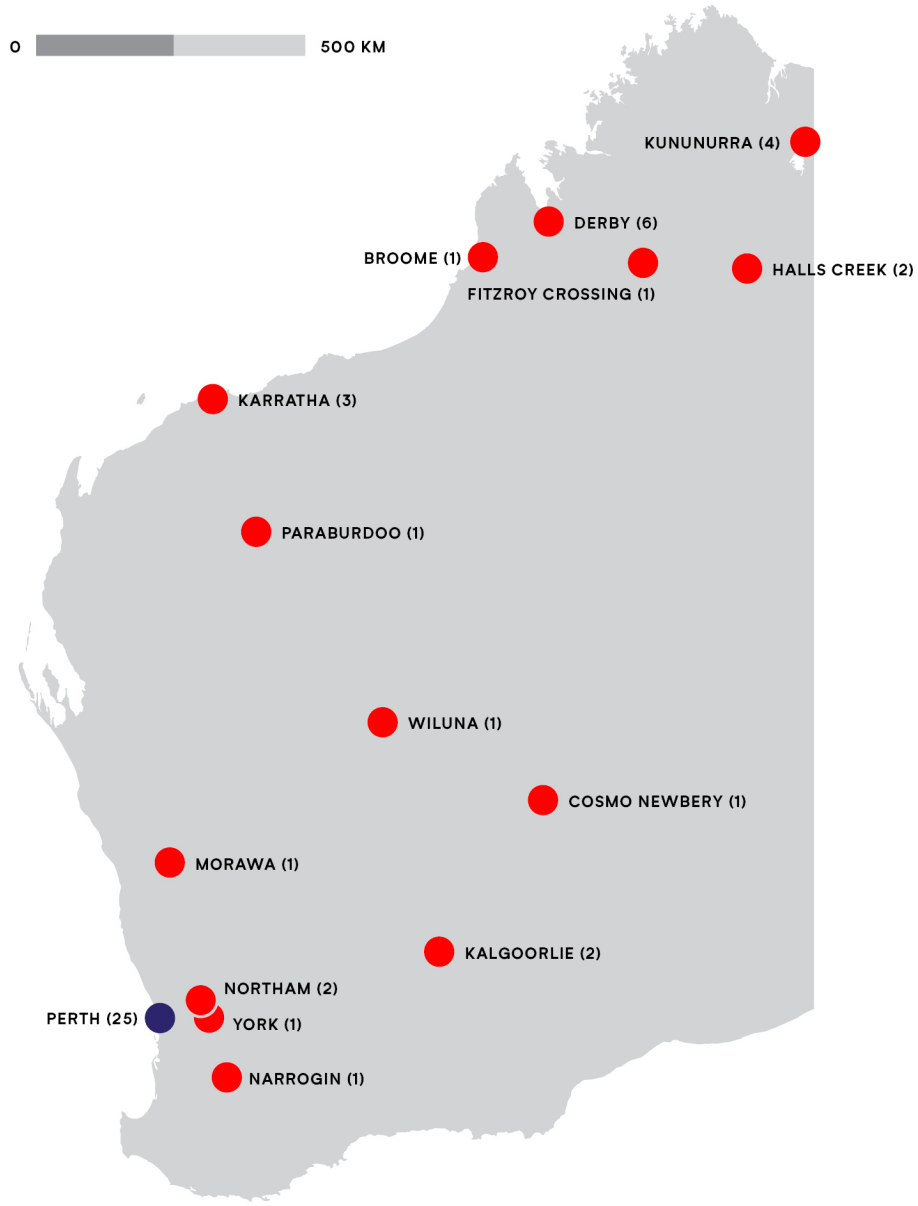
Item	Description
1	Study approval from an Aboriginal Health Ethics Committee and formal endorsement from all participating Aboriginal Medical Services (AMS).
2	Provision of free, safe and effective (non-experimental) treatment.
3	Treatment of participants within their local AMS facility where possible.
4	Collaboration with established ophthalmology outreach services (Lions Outback Vision in Western Australia).
5	Involvement of Aboriginal Liaison Officers to support participants.
6	Provision of free transport, appointment reminders and other non-clinical support for participants.
7	Access to timely cataract surgery in both remote and metropolitan locations at no expense to participants.

8	Collaboration with established visiting optometry services to remote areas, including the use of teleophthalmology for case discussion.
9	Cultural safety training for all trial staff, with the aim of improving the quality of service provided to Aboriginal people.
10	Research leadership from clinicians with fellowship training in Aboriginal eye care (HR, AT) and relevant clinical subspecialties (HR).

2.2 Participants

From June 2017 to March 2019, a total of 62 eyes were screened for eligibility. Eligibility criteria included patients who self-identified as Aboriginal, aged ≥18 years with DMO involving the central macula as confirmed by clinical examination and imaging of the retina with spectral domain macular ocular coherence tomography (SD-OCT), as well as Snellen best corrected visual acuity (BCVA) of 6/9 (0.2 LogMAR, 75 letters) or worse in the study eye. Both phakic and pseudophakic patients were enrolled. A complete list of inclusion and exclusion criteria is available online as supporting information. Participants were recruited from metropolitan and remote sites throughout Western Australia, at clinics and AMS providers that receive ophthalmology visits. 'Metropolitan' and 'remote' were defined by the Australian Statistical Geography Standard Remoteness Structure.[13] Metropolitan participants were located in the capital city of Perth, while remote participants were in 14 towns in the Kimberley, Pilbara, Mid-West, Wheatbelt and Goldfields regions (Figure 1). All eligible participants signed written informed consent prior to randomization and treatment.

Figure 1: Recruitment sites and numbers of eyes at each site.



2.3 Randomization and masking

Patients were screened at routine ophthalmology outpatient appointments. Those who met the eligibility criteria and consented to trial enrolment were randomized using a true random number generator by the trial coordinator.[14] Randomised participants were allocated to receive either bevacizumab 1.25 mg/0.05 mL or the

0.7 mg DEX-implant on a 1:1 basis. Each participant received a unique identification number. Both eyes were enrolled if they met the eligibility criteria for the study. The treating investigators were unmasked as medications were provided in their original syringes, while patients were masked to the treatment allocation.

2.4 Procedures

Participants received their first injection at a baseline visit. Drug administration was based on a predetermined fixed regime of monthly injections for bevacizumab and 3-monthly injections of the DEX-implant. Bevacizumab was chosen as it was readily available at all participating sites, and (unlike ranibizumab or aflibercept) does not require a PBS application. The three-monthly (rather than 4, 5 or 6-monthly) regimen with the DEX implant was chosen due to the expected level of non-attendance among participants, thus providing more opportunities for treatment during the study. Injections into the vitreous were performed under sterile conditions as an outpatient procedure, using best practice guidelines. All participants were scheduled for monthly review visits over the study period. At every visit, BCVA, intraocular pressure (IOP) measurement, dilated fundus examination and and SD-OCT were performed. Snellen charts were used due to their availability at all sites (ETDRS and LogMAR charts were only available at one site). OHT requiring treatment was defined as an IOP ≥28 mmHg, and treated with topical pressure-lowering drops. Participants were withdrawn if the IOP remained elevated despite drops, if there was noncompliance with topical treatment, or if there was a single IOP measurement ≥40 mmHg. Most sites used the 3D Macula Analysis scan on the Topcon Maestro OCT machine (Topcon Corporation Tokyo, Japan). The Heidelberg Spectralis (Heidelberg Engineering, Heidelberg, Germany) system was available at one site in Perth.

With regard to lens status, both pseudophakic and phakic eyes were eligible for enrolment, with no eyes were excluded due to lens status. As per the Pharmaceutical Benefits Scheme (PBS) guidelines, cataract surgery was arranged for all phakic participants who received the DEX-implant. For participants receiving bevacizumab, the decision to perform cataract surgery was made along conventional

lines, through clinical grading of the cataract plus discussion with the patient, taking into account the BCVA in both eyes.

2.5 Outcomes

The primary outcome was the difference in the BCVA from 0-12 months between treatment arms, with a non-inferiority margin of 0.1 LogMAR (equivalent to 5 letters). Secondary visual outcomes included the proportion of participants with a BCVA loss or gain of LogMAR ≥ 0.3 (15 letters); change in central macular thickness (CMT) measured by SD-OCT, the mean number of injections per participant, and the number of scheduled appointments attended by the participants in each group. Safety measures included the change in mean IOP, and the number of participants with one or more occasions of OHT (defined as any IOP elevation >28 mmHg, or an increase in IOP of >10 mmHg from baseline) requiring medical, laser or surgical treatment. Adverse events (AEs), serious adverse events (SAEs) and serious adverse reactions (SARs) were coded according to the National Medical Research Council (2016) safety monitoring and reporting in clinical trials definitions.[15]

2.6 Statistical Analysis

The sample size for determining 80% power of non-inferiority by excluding a difference in the mean change in BCVA between treatment arms of 20% (equivalent to 0.1 LogMAR, or 5 letters) with a one-sided alpha significance level of 0.05% was calculated to be 50 eyes. Statistical analysis was based on the intention-to-treat principle and the analysis database was set up with all missing BCVA values imputed by multiple imputation with linear regression to account for intra-eye (within patient) correlation, using the Stata V16.1 (Stata Corp, Texas, United States of America, 2019) data augmentation algorithm to generate 30 imputed data sets. Rubin's formulas were used to combine the observed parameter estimates and standard errors into a single set of results which reproduce the variability had the data been complete.[16] Snellen visual acuity measurements were converted to a LogMAR score and letters for statistical analysis and reporting. In order to be included in the analysis, participants had to have at least one visit after the initial baseline measurement. Non-inferiority was tested using a 1-sided t test. The DEX-implant

was considered non-inferior to bevacizumab if the upper bound of the 2-sided 90% confidence interval (CI) of the difference in BCVA change between treatment arms from 0-12 months did not exceed the non-inferiority margin of 0.1 LogMAR (5 letters). Analyses of all the other continuous variables in the trial were carried out using 2-sided t tests. Proportions were tested using Fisher's exact tests, as frequencies in some cells were <5. The analysis of the influence of cataract surgery during the trial was conducted using covariance analysis (ordinary least squares regression), with the inclusion of a binary adjustment variable to indicate whether the patient had surgery during the trial period. Subgroup analyses were carried out for metropolitan and remote locations. For all statistical tests, a significance level of 0.05 was applied. All the analyses were conducted using Stata V16.1.

2.7 Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

3. RESULTS

From July 25, 2017, to March 28, 2019, 62 eyes of 46 participants were assessed for eligibility. Of these, 58 eyes were eligible and were randomized to receive either the DEX-implant (n=27) or bevacizumab (n=31). Four eyes (one randomised to bevacizumab and three to the DEX-implant) were withdrawn after only attending the baseline visit. One participant receiving bevacizumab developed endophthalmitis in one eye and subsequently withdrew both eyes of their own accord. Fifty-two eyes of 38 participants (24 DEX-implant, 28 bevacizumab) were included in the final analysis (Figure 2, Table 2). The trial concluded once the last participant completed their 12-month follow-up visit.

Figure 2: Flow diagram of participants through the study.

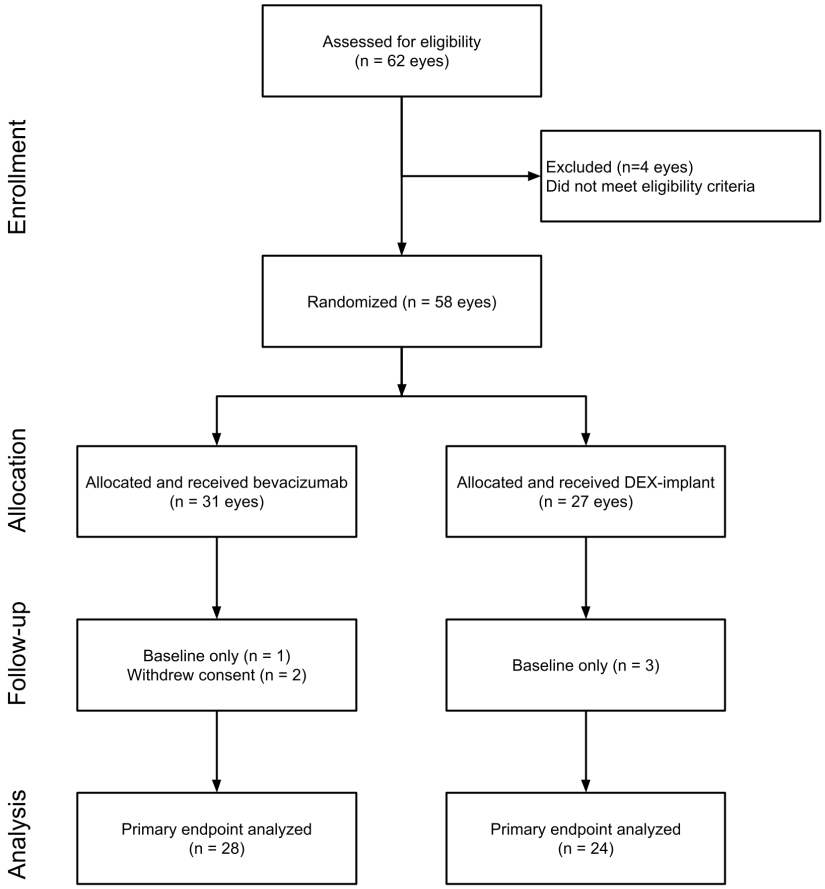


Table 2: Characteristics at baseline

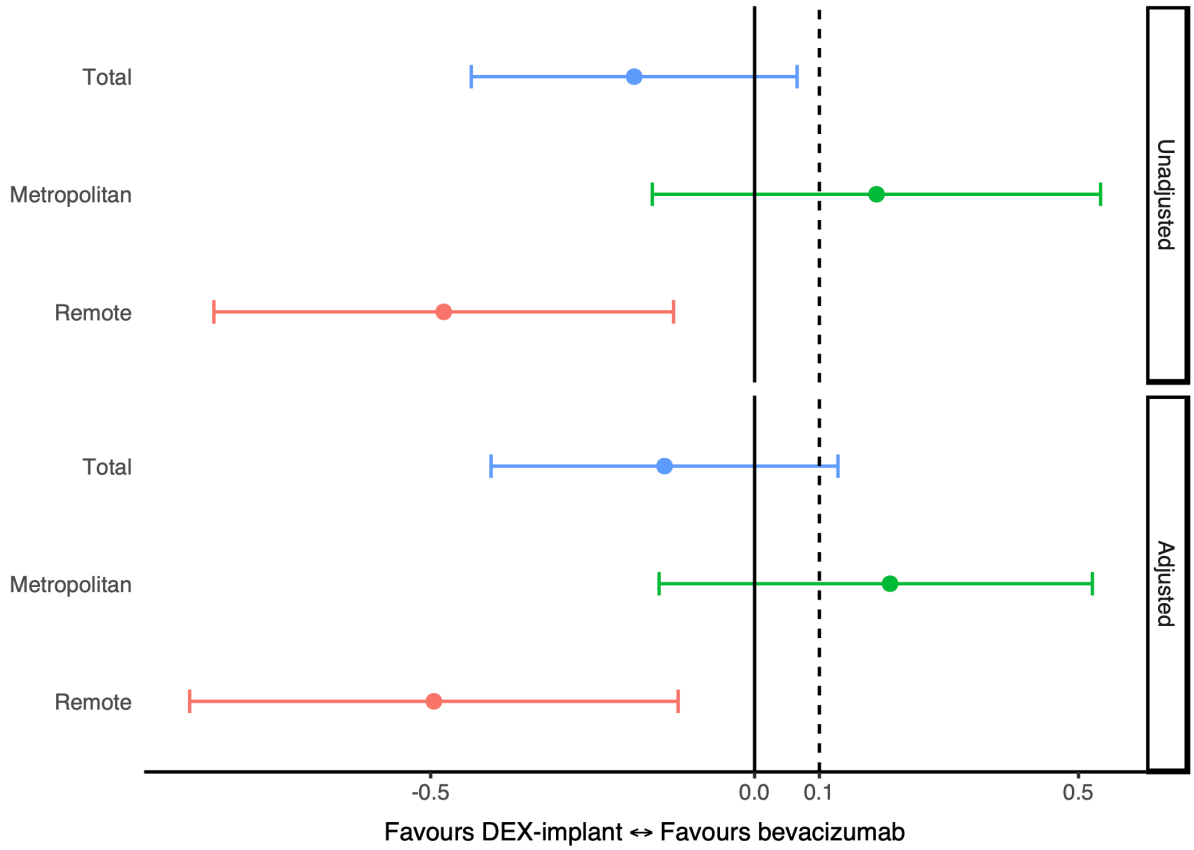
Characteristic	**DEX-implant (n=24)**	**Bevacizumab (n=28)**
Age, years	59.4 (8.0)	60.8 (5.8)
Female sex, n (%)	18 (75%)	17 (61%)
BCVA, LogMAR, letters	0.42 (0.2), 64	0.46 (0.4), 62
CMT, µm (SD)	400 (103.9)	404 (135.4)
IOP, mmHg (SD)	12.4 (3.6)	13.5 (4.1)
Location, n (%)		
Regional	13 (54%)	12 (43%)
Metropolitan	11 (46%)	16 (57%)
Lens status, n (%)		

Phakic	15 (65%)	21 (72%)
Pseudophakic	8 (35%)	8 (28%)
Duration of diabetes, years	11.1 (7.2)	12.4 (7.4)
Glycosylated haemoglobin, %	8.4 (2.0)	8.5 (2.2)

Data are mean (standard deviation) unless otherwise indicated.

For the total cohort, before adjusting for cataract surgery, the upper bound of the two-sided 90% CI of the difference in the BCVA change was 0.07 LogMAR (3.5 letters), confirming the non-inferiority of the DEX-implant to bevacizumab (Figure 3, Table 3). Ten (45%) participants in the DEX-implant group and seven (27%) in the bevacizumab group had cataract surgery during the 12-month trial period. After adjusting for the effect of cataract surgery, the DEX-implant was inferior to bevacizumab, with the upper bound of the 90% CI increasing to 0.13 LogMAR (6.5 letters), just exceeding the non-inferiority margin of 0.1 LogMAR (5 letters; Figure 3).

Figure 3: The difference in the mean change in BCVA (LogMAR) from 0-12 months between the treatment groups.



The solid dots are means; the plot whiskers are 90% confidence intervals; the dashed line indicates the non-inferiority margin of 0.1 LogMAR (5 letters). Adjusted results are for those that received cataract surgery during the trial.

Table 3: Primary and secondary outcomes

Outcomes	**DEX-implant (n=28)**	**Bevacizumab (n=24)**	**Upper bound 90% CI**[†]
Primary			
Change in BCVA, 0-12 months, letters	4.0 (4.0)	-5.5 (6.0)	0.07
Month 3	-4.0 (5.5)	0 (0.5)	0.32
Month 6	3.0 (3.5)	0 (0.5)	0.17
Month 9	5.0 (4.0)	1.0 (5.0)	0.14
Final BCVA at 12 months, LogMAR, letters	68 (2.5)	56.5 (4.5)	
Secondary			P-value
Change in BCVA, n (%)			0.75
Loss or gain < 15 letters	20 (80%)	19 (70%)	
Gain of ≥ 15 letters	3 (12%)	4 (15%)	
Loss of ≥ 15 letters	2 (8%)	4 (15%)	
Change in CMT, 0-12 months, µm	-61.2 (35.7)	-28.7 (30.8)	0.48
Month 3	-66.8 (33.8)	-3.8 (37.8)	0.23
Month 6	-83.8 (32.6)	-6.5 (42.1)	0.09
Month 9	-94.7 (26.9)	-35.1 (31.9)	0.15
Final CMT at 12 months, µm	332 (150.9)	381 (129.8)	0.21
Number of injections, n	3.3 (1.2)	7.2 (3.8)	< 0.001
Number of attendances, n	9.4 (3.96)	8.0 (4.4)	0.22

Data are mean (standard deviation) unless otherwise indicated.

[‡] Upper bound of the 2-sided 90% confidence interval (CI) of the difference in BCVA change between treatment arms from 0-12 months.

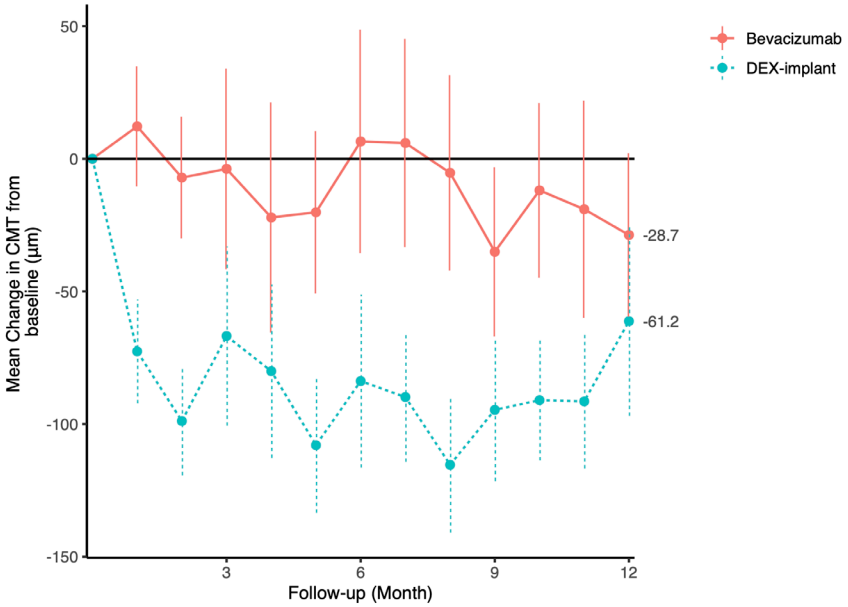
Overall, the BCVA improved by 4.0 letters (LogMAR 0.42 to 0.34) in the DEX-implant group, and declined by 5.5 letters (LogMAR 0.46 to 0.57) in the bevacizumab group. There was no significant difference between groups in the proportion of participants whose BCVA improved or declined by <15 letters or ≥ 15 letters (P= 0.75).

3.1 Central Macular Thickness

At 12 months, the mean CMT decreased by 61μm and 29μm amongst the DEX-implant and bevacizumab participants, respectively (P=0.48). For the DEX-implant group, the CMT of peaked at the 3-, 6-, 9- and 12-month marks, indicating the time points that the therapeutic effect wore off. The mean CMT and mean change in CMT from baseline was lower for the DEX-implant group at every time point (Table 2 and Figure 5).

Figure 4: Mean change in CMT for (A) all, (B) metropolitan and (C) remote participants.

(A)



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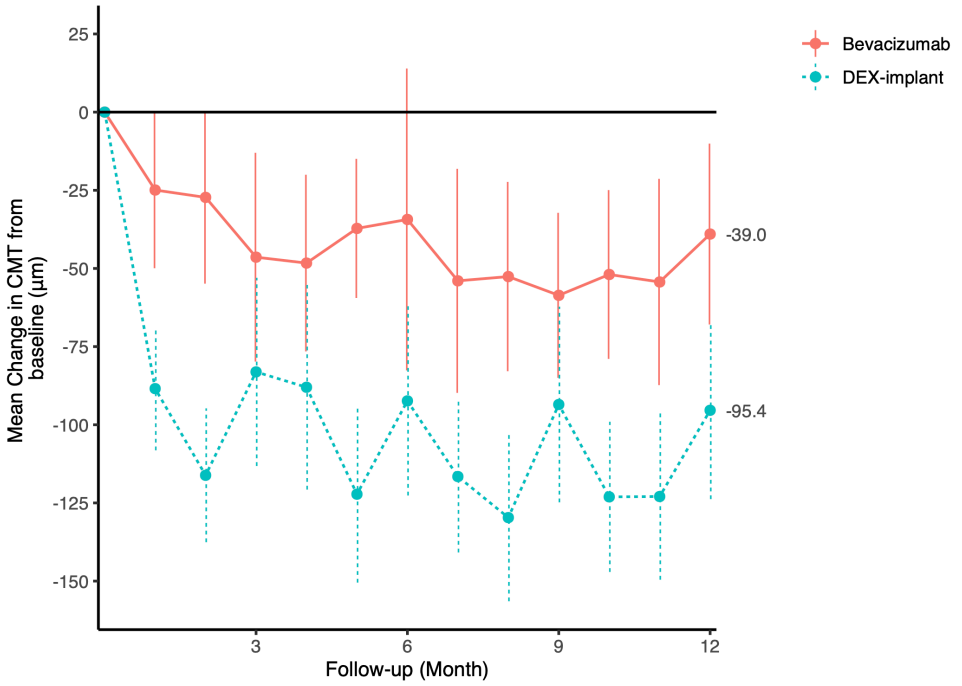

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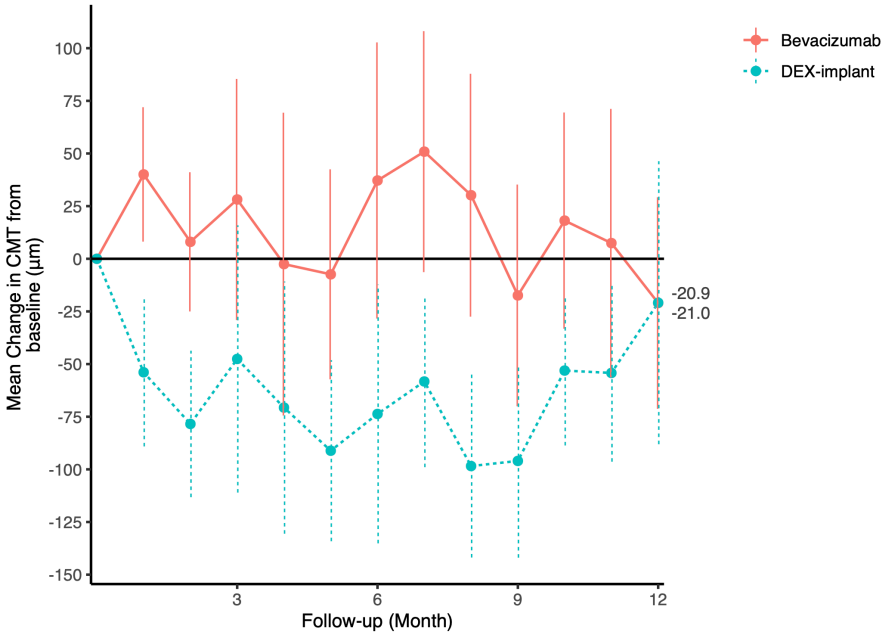


3.2 Number of injections and attendances

The mean number of injections received over the 12 months was 7.2 and 3.3 in the bevacizumab and DEX-implant groups, respectively (Table 3). When considered as a proportion of the predetermined regime of 12 bevacizumab and four DEX-implant injections, the DEX-implant group was closer to achieving the intended number of injections (82.5% versus 60% for bevacizumab; P<0.001). This was evident in both

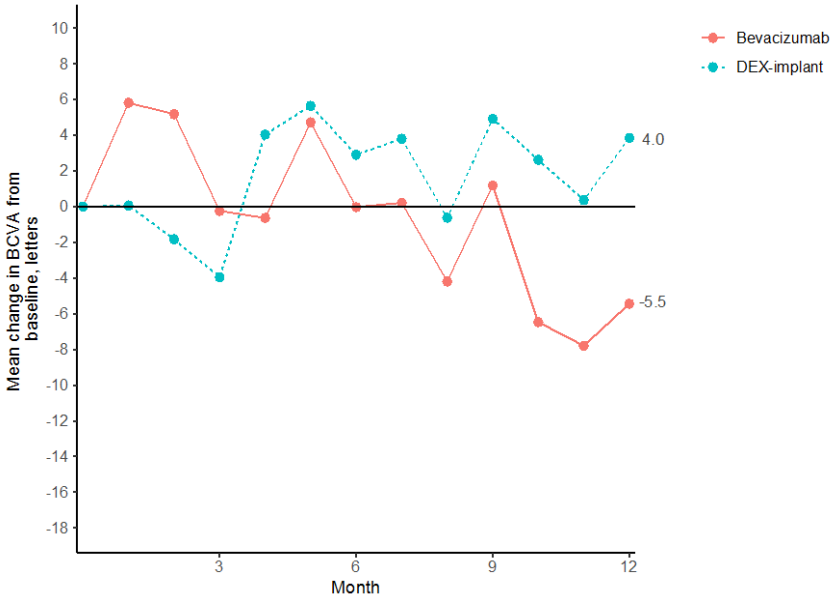
metropolitan (92.3% vs 79.8%, P<0.001) and remote (68.0% vs 45.3%, P<0.001) participants. There was no difference between the treatment groups in the number of visits that were attended (P=0.22), but attendance was significantly higher for metropolitan compared to remote participants (11.3 versus 6.2, respectively; P<0.001).

3.3 Metropolitan versus remote participants

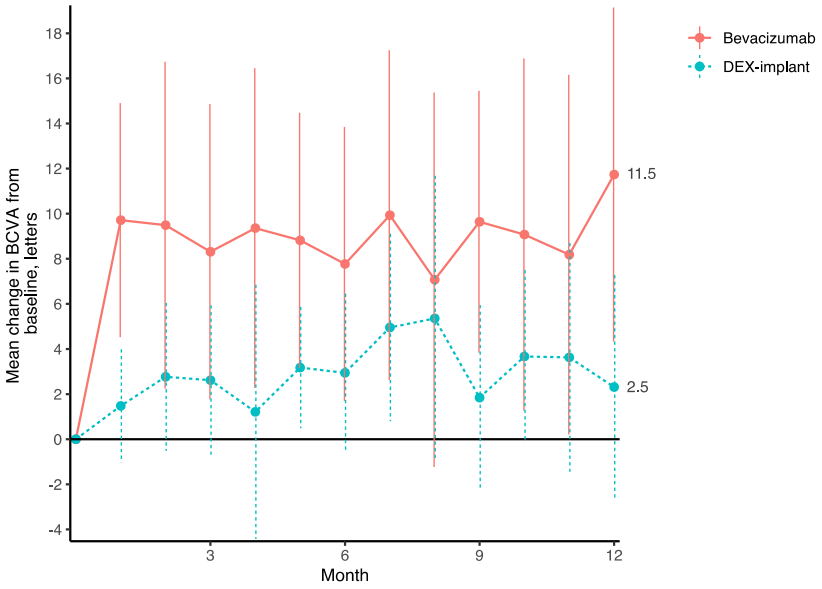
For remote participants, a regression of the change in BCVA adjusted for cataract surgery was 24 letters (LogMAR 0.48) in favour of the DEX-implant, which surpassed non-inferiority to achieve superiority to bevacizumab (95% CI 0.87, 0.12; Figures 3 and 5, Table 4). Among metropolitan participants, BCVA improved by 2.5 and 11.5 letters in the DEX-implant and bevacizumab groups, respectively, leading to a similar final vision at 12 months (P=0.58). The larger improvement in BCVA among metropolitan patients receiving bevacizumab may therefore have been due to their lower vision at baseline (58.5 letters), compared to the baseline vision of metropolitan patients who received the DEX-implant (67.0 letters).

Figure 5: Change in BCVA for (A) all, (B) metropolitan and (C) remote participants.

(A)



(B)



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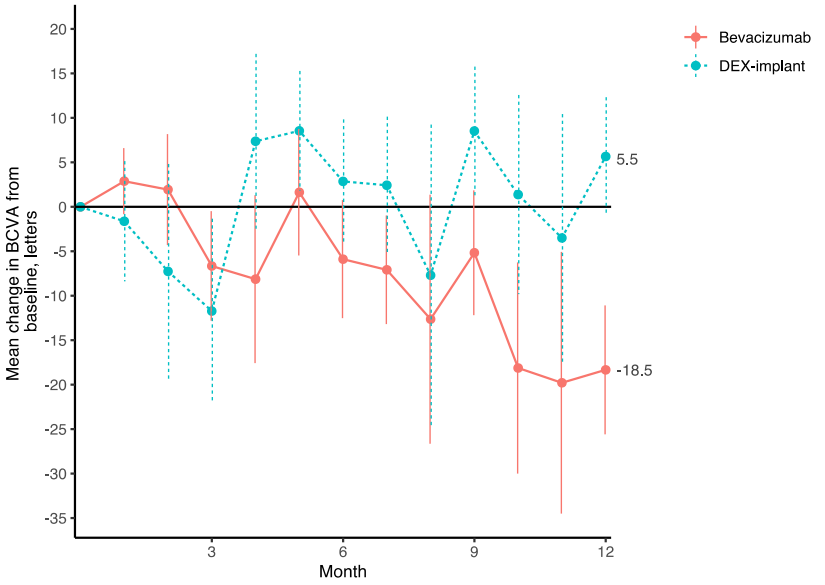

Table 4: Sub-analysis of metropolitan and remote participants

Outcomes	Metropolitan (n=25)			Remote (n=27)		
	DEX-implant (n=13)	Bevacizumab (n=12)	Upper bound 90% CI	DEX-implant (n=11)	Bevacizumab (n=16)	Upper bound 90% CI
Primary						
Change in BCVA, 0-12 months, LogMAR, letters	2.5 (0.5)	11.5 (7.5)	0.53	5.5 (6.5)	-18.5 (7.5)	-0.13
			P-value			P-value
BCVA at baseline, LogMAR, letters	67 (8.5)	58.5 (27)	0.31	61 (12.5)	64.5 (9.5)	0.38
BCVA at 12 months, LogMAR, letters	69.5 (10.5)	70 (11)	0.58	66.5 (12.5)	46 (27)	0.04
Secondary						
Mean CMT at baseline, µm	428.5 (113.7)	446.5 (162.4)	0.75	366.0 (83.64)	372.6 (105.6)	0.60
Change in CMT from 0-12 months, µm	-95.4 (28.4)	-39.0 (28.9)	0.16	-20.9 (67.2)	-21.0 (50.2)	0.99
CMT at 12 months, µm	328 (106.0)	404 (163.7)	0.18	336 (197)	363 (99.5)	0.64
Number of injections, n (%)	3.7 (1.0)	9.6 (4.4)	0.0001	2.7 (1.2)	5.4 (1.9)	0.0003

Number of attendances, n (%)[†]	11.5 (2.7)	11.1 (4.8)	0.81	7.0 (3.9)	5.6 (1.96)	0.24

Data are mean (standard deviation) unless otherwise indicated.

[†]Overall mean attendance was 11.1 and 6.0 for metropolitan and remote participants, respectively.

3.4 Ocular adverse events

There were eight incidences of OHT in seven participants who received the DEX-implant (33.3% of DEX-implant eyes), requiring treatment with IOP-lowering drops (Table 5). Two participants who received the DEX-implant developed an IOP of >40 mmHg and were withdrawn from the trial after receiving pressure-lowering medication. All cases of OHT were managed with topical drops only, with none requiring laser or surgical treatment. One participant receiving bevacizumab developed endophthalmitis. There was one death; the cause was unknown to the patient's AMS provider.

Table 5: Ocular adverse events

Event	DEX-implant (n=24)	Bevacizumab (n=28)
IOP elevation >10 mmHg from baseline	10 (42)	0 (0)
IOP >28 mmHg at any visit	2 (8)	0 (0)
IOP >40 mmHg at any visit	2 (8)	0 (0)
Participants requiring IOP-lowering drops	8 (33)	0 (0.0)
Participants requiring laser or incisional glaucoma surgery	0 (0)	0 (0)
Endophthalmitis	0 (0)	1 (3.5)
Herpes simplex keratitis	1 (4)	0 (0)
Hyphema	0 (0)	1 (3.5)
Lens trauma	1 (4)	0 (0)
Anterior uveitis	0 (0)	1 (3.5)

Data are n (%)

3.5 Cataract surgery

Thirty-nine of the 52 study eyes (75.0%) were phakic at baseline. Sixteen of these were in the DEX-implant arm (66.7% of all eyes in this group), of which 10 (62.5%)

underwent cataract surgery. Twenty-three eyes in the bevacizumab arm (82.1%) were phakic at baseline, of which 7 (30.4%) underwent cataract surgery. After cataract surgery, the mean BCVA improved by 16.5 letters (LogMAR 0.62 to 0.29) for the total cohort, and by 18.5 and 14 letters (LogMAR 0.65 to 0.28, and 0.59 to 0.31) for the DEX-implant and bevacizumab groups, respectively (P=0.71).

4. DISCUSSION

This study found that, when combined with cataract surgery, the DEX-implant was non-inferior to bevacizumab (upper bound of the 90% CI of 0.07 LogMAR, equivalent to 3.5 letters) for the treatment of DMO among Aboriginal participants. Overall, the mean BCVA improved by 4.0 letters in the DEX-implant group (from a mean Snellen acuity of 6/15- at baseline, to 6/12- at 12 months), and declined by 5.5 letters in the bevacizumab group (from 6/15+ at baseline to 6/24+ at 12 months). This meant that, on average, participants who received the DEX-implant met the visual requirement for a private driver's license at 12 months, whilst those who received bevacizumab did not. The visual gain provided by the DEX-implant was comparable to that found in the BEVORDEX study, which showed an improvement of 5.6 letters among non-Aboriginal Australians after one year of treatment.[17]

After adjusting for the effect of cataract surgery, the DEX-implant failed to meet the upper bound of the 90% confidence interval for non-inferiority, exceeding it by 1.5 letters. This means that, while the DEX-implant achieved better mean BCVA overall (both with and without adjustment for cataract surgery), the distribution of results gained from the DEX-implant were not statistically better *enough* than bevacizumab to conclude with sufficient certainty that the findings weren't due to chance. A pragmatic interpretation of these results that real-world patients who receive the DEX-implant are likely, on average, to achieve better visual improvement after 12 months of treatment, provided they have access to timely cataract surgery. In the absence of cataract surgery, a proportion of these patients will have worse visual outcomes than patients who receive bevacizumab. This situation may differ for patients living in remote locations, in whom the DEX-implant achieved superior

visual results than bevacizumab in this study, irrespective of cataract surgery (P=0.04). Access to cataract surgery, and the results for patients in remote locations, are further discussed below.

In line with visual acuity outcomes, there were larger decreases in CMT in the DEX-implant group (-61µm versus -29µm). These findings are similar to those of the BEVORDEX study, which found reductions of -187 µm and -122µm at 12 months, respectively.[17] A meta-analysis has shown that with longer intervals between injections, the CMT gains conferred by the DEX-implant may not be sustained at 12 months.[18] These findings support a 2- to 4-monthly injection schedule for the DEX-implant, which may be considered achievable for many outreach ophthalmology services in Australia.

In the DEX-implant group, the incidence of OHT requiring treatment was 33.3%, which is comparable to previous studies which have reported rates between 31% to 44%.[17, 19] At 12 months, the mean IOP increased by 6.5 mmHg in the DEX-implant group (P=0.001) and was 5.0 mmHg higher than the bevacizumab group (P=0.002). Among participants who developed OHT, compliance with topical pressure-lowering drops was variable, despite the provision of culturally appropriate instructions, free medication and close follow-up. No participant required incisional glaucoma surgery, and the IOP returned to normal in 1-4 months in all participants. The timing of the IOP rise is a consideration in safety monitoring, with mean IOP peaks occurring around 6 weeks after administration of the DEX-implant.[19] Similarly, most peaks in our study occurred at 6 to 8 weeks, meaning that IOP monitoring is required more regularly than the dosing interval. We recommend the judicious use of the DEX-implant in Aboriginal patients who may be more able to comply with pressure lowering drops, in settings where timely follow-up of IOP is possible.

In Australia, the limited available evidence suggests a lower prevalence of glaucoma among Aboriginal people, compared to non-Aboriginal people.[20-22] This is the first study, to our knowledge, to report steroid-induced OHT in Aboriginal people, finding it to be comparable to that reported in non-Aboriginal people. Another risk arising

from longer term monotherapy with the DEX-implant is the development of proliferative diabetic retinopathy.[23] Caution should therefore be exercised in using the DEX-implant among Aboriginal patients with limited access to regular examination and retinal laser treatment.

Pharmaceutical regulatory requirements in Australia require that the DEX-implant is used in pseudophakic patients, or phakic patients who are scheduled for cataract surgery.[24] As expected, more patients in the DEX-implant arm (n=10, 62.5% of phakic eyes at baseline) had cataract surgery than those in the bevacizumab arm (n=7, 30.4% of phakic eyes at baseline). The improvement in vision after cataract surgery in this study (16.5 letters) was relatively high, compared to other studies that have assessed cataract surgery in eyes with DMO. This may be due to the higher grade of lens opacity, and worse presenting vision at the time of surgery, reported in Aboriginal compared to non-Aboriginal people.[25] Five phakic patients who received the DEX-implant did not receive cataract surgery within the 12-month study period, due to transport and logistical barriers. This finding signals the need for caution regarding the use of the DEX-implant in phakic patients who may have limited access to cataract surgery. The need to improve access to cataract surgery for Aboriginal people in Australia remains an ongoing priority.[26]

To our knowledge, this is the first ever ophthalmic randomized controlled trial (RCT) to exclusively recruit Aboriginal or Indigenous participants. The historical barriers to performing this form of research have included a lack of endorsement from local health services, lack of Aboriginal staff champions, and the challenges of adhering to trial-related procedures.[12] We propose that the ten enablers incorporated in our study design provide a framework for performing future ophthalmic research in Aboriginal communities (Table 1), with consideration given to input from patients themselves through community-controlled research models.[27]

As this trial progressed, a disparity was observed between the results of participants in metropolitan and remote locations. This prompted a post-hoc analysis of results by location, which found that, among remote participants, the DEX-implant provided

a 24 letter relative gain over bevacizumab (final visions of 6/15+ versus 6/38+, respectively). This surpassed non-inferiority to achieve superiority (P=0.04), and is likely to be attributable to the higher proportion of the intended treatments (four for DEX-implant, 12 for bevacizumab) that participants received. On average, remote participants received a total of 2.7 DEX-implant and 5.4 bevacizumab injections, equivalent to 68% and 45.3% of their intended total treatments (P<0.001). Remote participants also attended significantly fewer visits than their metropolitan counterparts (6.2 vs 11.3, P<0.001). This combination of fewer attendances, fewer injections and superior clinical outcomes in remote areas suggests that the DEX-implant has the potential to reduce vision loss from DMO in these communities. These findings may be generalizable to other jurisdictions with Indigenous populations, such as the USA, Canada and New Zealand.[8,9]

Among metropolitan participants, bevacizumab showed a non-statistically significant advantage over the DEX-implant in terms of the change in BCVA (+11.5 versus +2.5 letters, respectively). In our study, the baseline vision among metropolitan patients receiving bevacizumab was 58.5 letters, which was lower than the 67 letters at baseline for DEX-implant participants. This may have created a higher potential for visual improvement among bevacizumab patients, thereby overstating the efficacy of bevacizumab, given that both treatment groups finished with a near identical BCVA at 12 months (70 versus 69.5 letters). Nonetheless, when given frequently, bevacizumab may provide marginally superior visual gains, as found in the BEVORDEX study, which found 8.9 and 5.6 letter gains for the bevacizumab and DEX-implant, respectively (P=0.24). Additionally, metropolitan participants in our study attended 11 of 12 scheduled appointments and received of 10 of 12 (83.3%) intended treatments. These findings suggest that, among metropolitan Aboriginal patients who are able to attend regular appointments, anti-VEGF injections can reasonably be retained as the first-line treatment for DMO, particularly in phakic patients.

A limitation of this study was the 50% attendance of study visits by remote participants. Furthermore, 36 of the 52 study eyes (69.2%, hereby referred to as

'Completers'), attended the final 12-month visit, meaning that almost one third of study eyes were deemed 'Non-completers'. This was an unsurprising finding, given that healthcare attendance by Aboriginal people is historically variable due to cultural, language and other barriers.[28] To counter these trends, participants in this study were provided with personal reminders, free transport, and dedicated non-clinical support to enable attendance (Table 1). A sensitivity analysis of the baseline characteristics of 'Completers' versus 'Non-Completers' revealed no significant differences between these groups (available online as supporting information). Furthermore, the number of anti-VEGF injections received by remote participants in this study (5.1) was substantially higher than in real-world practice, where previous audits have demonstrated an average of 2.8 injections per year.[7] Whilst the sub-analysis of metropolitan versus remote participants achieved statistically significant results, these should be interpreted with caution due to the modest numbers of participants involved.

4.1 Conclusion

When combined with timely cataract surgery, the DEX-implant is a viable alternative to anti-VEGF therapy for Aboriginal patients with DMO. This may be particularly relevant in remote areas, where the DEX-implant achieved superior visual outcomes to bevacizumab in this study, irrespective of phakic status. Visual gains should be balanced against the risk of steroid-induced ocular hypertension, which occurred in one-third of participants who received the DEX-implant. This study provides a framework for performing future ophthalmic research in Aboriginal and Indigenous communities, in Australia and overseas.

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