Bioscientia Medicina: Journal of Biomedicine and Translational Research
https://bioscmed.com e-ISSN: 2598-0580 Vol. 10, No. 3 (2026)

ORIGINAL ARTICLE

Feasibility, Visual Outcomes and Severity-Stratified Response to Pre-operative Intravitreal Bevacizumab Before Vitrectomy in Proliferative Diabetic Retinopathy

Ramzi Amin[1*], Fajar Prasetya[1], Abdul Karim Ansyori[1]

[1]Department of Ophthalmology, Faculty of Medicine, Universitas Sriwijaya/ Dr. Mohammad Hoesin Central General Hospital, Palembang, Indonesia

ARTICLE INFO

Article history
Received: February 15, 2026
Accepted: March 1, 2026
Published: March 29, 2026

Keywords:
Bevacizumab
Feasibility studies
Pars plana vitrectomy
Proliferative diabetic retinopathy
Vitreous hemorrhage

**Corresponding author:*
Ramzi Amin
ramziamin20@gmail.com
ORCID: 0000-0003-1339-7580

DOI:
https://doi.org/10.37275/bsm.v10i3.1664

ABSTRACT

Background: Proliferative diabetic retinopathy is a leading cause of vision loss in working-age Indonesians, and pre-operative anti-vascular endothelial growth factor therapy has been proposed to make vitrectomy safer, yet Southeast Asian trial evidence is almost absent.

Objective: To assess the feasibility, visual outcomes, and severity-stratified response to pre-operative intravitreal bevacizumab before 23-gauge pars plana vitrectomy in patients with proliferative diabetic retinopathy.

Methods: In a single-centre, single-blind pilot randomised controlled trial at the Department of Ophthalmology, Faculty of Medicine, Universitas Sriwijaya/ Dr. Mohammad Hoesin Central General Hospital, Palembang (July–November 2025), 21 adults with proliferative diabetic retinopathy and non-clearing vitreous haemorrhage were allocated 1:1, stratified by haemorrhage severity, to intravitreal bevacizumab 1.25 mg/0.05 mL given 3–7 days before 23-gauge pars plana vitrectomy (n = 11) or to vitrectomy alone (n = 10). Progression criteria were pre-specified; the clinical outcome was best-corrected visual acuity change in LogMAR at one week.

Results: All progression criteria fell in the green zone (recruitment 95.5%, 95% CI 78.2–99.2; retention and adherence 100%). Bevacizumab-treated eyes gained more vision, but imprecisely (Hodges–Lehmann shift 0.35 LogMAR, envelope 0.10 to 0.50; Hedges' g 0.65), the trial retaining only 14.8% power for the observed difference. Baseline vitreous haemorrhage severity dominated visual gain (adjusted B -0.397 LogMAR per grade, 95% CI -0.639 to -0.155; Cochran–Armitage trend p = 0.015).

Conclusion: Pre-operative bevacizumab is feasible in an Indonesian tertiary centre and warrants a severity-stratified multicentre trial.

1. Introduction

Diabetic retinopathy has become the only major cause of blindness whose age-standardised prevalence has risen over the past three decades, and it now affects roughly one in five adults living with diabetes worldwide.[1,2] The proliferative stage, defined by retinal or disc neovascularisation, accounts for a disproportionate share of severe vision loss because it culminates in non-clearing vitreous haemorrhage and tractional retinal detachment. Diabetes now affects 10.5% of adults aged 20–79 years worldwide, 536.6 million people in 2021 and a projected 783.2 million by 2045, with the steepest relative rise in middle-income countries such as Indonesia.[3] Community-based screening of 4251 Indonesians with type 2 diabetes in Greater Bandung found an age-standardised prevalence of any diabetic retinopathy of 30.7% and of vision-threatening disease of 7.6%.[4] Late presentation compounds that burden throughout the low- and middle-income world: at one tertiary eye centre 46.2% of all patients referred with diabetes already had proliferative disease.[5] Once the proliferative stage is reached it is the surgical rather than the medical arm of retinopathy care that carries the load, and the demand is cumulative — in a real-world series of 1094 vitrectomised patients the fellow eye also required vitrectomy in 31.0% by one year and 79.5% by ten years.[6]

The molecular driver of that surgical burden is well characterised. Chronic hyperglycaemia produces pericyte drop-out and capillary non-perfusion; the resulting inner-retinal ischaemia stabilises hypoxia-inducible factor 1α in Müller glia and retinal pigment epithelium, which in turn drives transcription of vascular endothelial growth factor A.[7,8] Vascular endothelial growth factor A both disrupts the blood–retinal barrier and induces endothelial sprouting into the posterior hyaloid, producing pericyte-poor, friable fronds that bleed under minimal traction. These membranes are precisely what the vitreoretinal surgeon must delaminate, which is why intra-operative bleeding, poor visualisation and iatrogenic retinal breaks cluster in eyes with the highest vascular endothelial growth factor load.[9,10] Spatial

pharmacokinetic modelling places the vitreous half-life of bevacizumab at approximately 5.4 days in the human eye, largely independent of the injection site.[11] Direct measurement gives the same answer from the biological side: vitreous vascular endothelial growth factor reaches its nadir five days after injection, whereas vitreoretinal fibrosis is significantly greater once seven days or more have elapsed.[8] Together these define a narrow pre-operative window in which neovascular tissue has involuted but fibrotic contraction has not yet supervened; Figure 1 sets out that causal chain and the pharmacokinetic window it creates.

Randomised evidence supports pre-operative anti-vascular endothelial growth factor pre-treatment for the operation, if not unambiguously for the eye. Pooling 17 randomised trials, pre-treatment reduced intra-operative vitreous haemorrhage (risk ratio 0.38, 95% CI 0.28–0.52) and iatrogenic retinal tears (risk ratio 0.56, 95% CI 0.43–0.72) and shortened operating time by 24.04 minutes.[12] A Cochrane synthesis of 28 trials and 1914 eyes reached the same conclusion from a different endpoint, halving early postoperative vitreous haemorrhage from 31% to 12% (risk ratio 0.44) and intra-operative breaks from 31% to 12% (risk ratio 0.37).[13] Randomised comparisons within the drug class find the available agents interchangeable as pre-treatment, and a randomised trial of prophylactic pre-operative injection lowered post-vitrectomy haemorrhage at one week from 39.3% to 14.8%; giving the drug before rather than during surgery shortened the operation from 74.49 ± 12.01 to 61.50 ± 11.44 minutes.[14,15,16] Against this, the DRCR Retina Network Protocol AB trial showed that the principal advantage of surgery over pharmacotherapy alone is speed rather than final acuity: median time to clearance of the vitreous haemorrhage was 4 weeks after vitrectomy against 36 weeks with anti-vascular endothelial growth factor alone.[17] Almost all of this evidence originates from East Asian, European and North American centres. Southeast Asian data are sparse, and this matters because anti-vascular endothelial growth factor injections already absorb 82.36% of the direct cost of diabetic retinopathy care in comparable middle-income systems, and health-economic modelling ranks bevacizumab-based pathways above ranibizumab- and aflibercept-based ones on net monetary benefit.[18,19]

Dr. Mohammad Hoesin Central General Hospital in Palembang is the referral centre for vitreoretinal surgery across South Sumatra, serving a catchment population of approximately eight million. Its case mix is dominated by late presentation: most eyes referred for vitrectomy already have haemorrhage dense enough to preclude panretinal photocoagulation, and many have never received laser treatment. Introducing a pre-operative injection step into that pathway is not a trivial protocol amendment; it requires an additional clinic visit, an additional sterile procedure, additional pharmacy handling of a compounded product, and a surgical slot booked to a 3–7-day window. Whether such a pathway can be delivered reliably in an Indonesian public tertiary centre is a feasibility question that must be answered before any efficacy question is worth asking.[20,21]

Two gaps therefore motivated this work. First, no published trial has tested the operational feasibility of a pre-operative bevacizumab pathway in Indonesia against pre-specified progression criteria. Second, existing surgical series rarely quantify how the benefit of pre-treatment varies with the density of the vitreous haemorrhage itself, even though haemorrhage grade is the single most accessible pre-operative prognostic marker in a setting without routine optical coherence tomography.[22] We therefore conducted a pilot randomised controlled trial with three aims: to test pre-specified feasibility progression criteria for a pre-operative bevacizumab pathway; to estimate, with confidence intervals and posterior probabilities rather than hypothesis tests, the magnitude of any early visual benefit; and to characterise the prognostic gradient across vitreous-haemorrhage severity so that a definitive trial can be stratified and powered rationally.

2. Methods

Study design and reporting

This was a single-centre, single-blind, parallel-group pilot randomised controlled trial with 1:1 allocation, reported in accordance with the CONSORT 2010 extension to randomised pilot and feasibility trials.[20] Consistent with that extension, the trial was designed to estimate feasibility parameters and effect sizes rather than to test an efficacy hypothesis; clinical outcomes are therefore reported as estimates with confidence intervals and posterior probabilities, and the significance testing performed by the original investigators is retained only for transparency.[23,24] The trial was conducted at the Department of Ophthalmology, Faculty of Medicine, Universitas Sriwijaya/ Dr. Mohammad Hoesin Central General Hospital, Palembang, Indonesia, a tertiary referral centre serving approximately eight million people in South Sumatra Province, between July and November 2025.

Participants

Consecutive adults aged 18–75 years with type 2 diabetes mellitus and proliferative diabetic retinopathy requiring urgent pars plana vitrectomy were screened. Inclusion criteria were proliferative disease with vitreous haemorrhage dense enough to preclude adequate panretinal photocoagulation or fundus imaging; no previous vitrectomy in the study eye; best-corrected visual acuity worse than 6/60 (LogMAR greater than 1.0); and capacity to give written informed consent and attend follow-up. Exclusion criteria were media opacity unrelated to vitreous haemorrhage; advanced glaucoma with intraocular pressure above 40 mmHg despite medical therapy; anti-vascular

endothelial growth factor injection within the preceding eight weeks; known hypersensitivity to bevacizumab; pregnancy or lactation; systemic contraindication to surgery (uncontrolled hypertension above 180/110 mmHg, myocardial infarction within three months, or active malignancy); and inability to attend scheduled review. One eye per participant was enrolled; where both eyes were eligible the eye with the denser haemorrhage was selected.

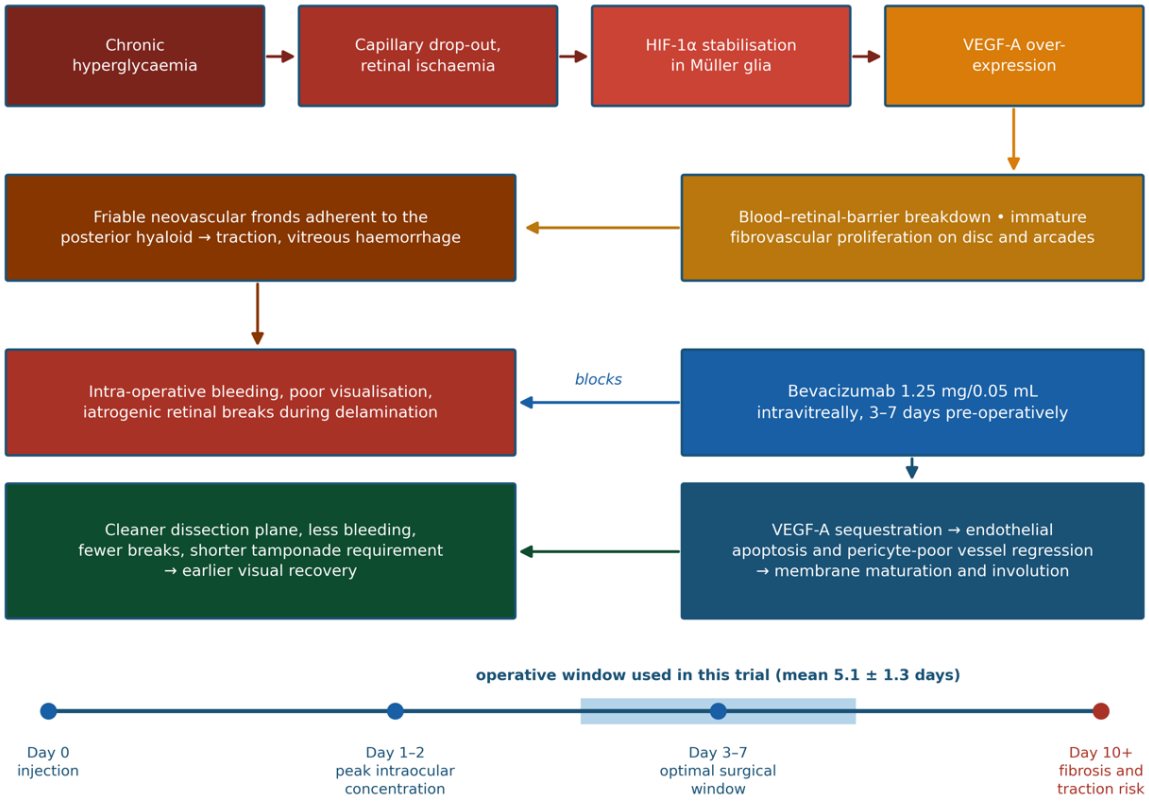

Figure 1. Molecular and surgical rationale for pre-operative vascular endothelial growth factor blockade in proliferative diabetic retinopathy. Hyperglycaemia-driven capillary drop-out stabilises hypoxia-inducible factor 1α and raises intraocular vascular endothelial growth factor A, producing friable fibrovascular membranes that bleed during delamination. The timeline shows the pharmacokinetic window exploited by a 3–7-day injection-to-surgery interval.

Randomisation, allocation concealment and masking

A computer-generated allocation sequence in a 1:1 ratio was produced with a secure web-based service and stratified by baseline vitreous-haemorrhage severity (mild or moderate versus severe), the strongest available prognostic factor. The sequence was generated and held by an independent research coordinator who took no part in clinical care or outcome assessment, and allocation was released only after eligibility had been confirmed and consent taken. Participants and the operating surgeon could not be masked because the intervention is an injection given days before surgery; the outcome assessor who performed all best-corrected visual-acuity refractions and secondary measurements was masked to allocation throughout.

Intervention and comparator

Participants allocated to the intervention received a single intravitreal injection of bevacizumab 1.25 mg in 0.05 mL of preservative-free phosphate-buffered saline, drawn from a compounded vial under aseptic pharmacy conditions, 3–7 days before scheduled vitrectomy (mean 5.1 ± 1.3 days). Injection followed a standard protocol: topical lidocaine 4%, povidone-iodine 5% preparation of the ocular surface and lids, sterile lid speculum, and a 27-gauge needle inserted 3.5–4.0 mm posterior to the limbus and directed towards the centre of the globe. Central retinal artery perfusion was confirmed clinically after injection. Comparator participants proceeded directly to vitrectomy with no sham injection.

Surgical technique

All procedures were performed by a single vitreoretinal surgeon with more than 15 years of experience, using a 23-gauge transconjunctival system (Constellation Vision System; Alcon, Fort Worth, TX, USA). The standardised sequence was core vitrectomy, peripheral vitreous-base shaving, systematic segmentation and delamination of fibrovascular membranes with intraocular forceps and vertical scissors, panretinal endolaser photocoagulation of 500–1000 applications, and tamponade with filtered air, sulphur hexafluoride or perfluoropropane selected

by the extent and location of retinal breaks or detachment. Intra-operative bleeding was graded on a three-point scale: grade 1, minimal and self-limiting; grade 2, moderate and requiring irrigation; grade 3, severe and requiring elevation of infusion pressure or temporary sclerotomy closure.

Vitreous-haemorrhage severity grading

Vitreous-haemorrhage severity was graded pre-operatively with a modified Teller classification combining slit-lamp examination and B-scan ultrasonography: mild, blood confined to the vitreous base with the peripheral retina visible; moderate, extensive blood obscuring most of the retina with an indistinct disc margin; and severe, a completely blood-filled vitreous cavity with no retinal detail resolvable on B-scan. Grading was performed before randomisation by the same masked assessor who later measured the outcomes, and the grade was used both as a randomisation stratum and as an ordinal covariate scored 0, 1 and 2.[22]

Outcomes and progression criteria

The feasibility outcomes, pre-specified with quantitative progression thresholds and a three-zone (green, amber, red) decision rule, were the recruitment rate (enrolled among eligible; green ≥80%, red <60%), the retention rate (attending the one-week review; green ≥90%, red <75%), treatment adherence (allocated injections delivered within the intended 3–7-day window; green ≥95%, red <80%) and outcome-data completeness (green ≥95%, red <80%).[21,25] The clinical outcome used to generate effect estimates was the change in best-corrected visual acuity in LogMAR units between the pre-operative visit and one week after surgery, measured by ETDRS protocol refraction. Secondary outcomes were operative duration in minutes, the number and location of iatrogenic retinal breaks, intra-operative haemorrhage grade, intraocular pressure on the first postoperative day and the distribution of tamponade agent. A responder was defined a priori as a gain of at least 0.30 LogMAR, three ETDRS lines. That threshold is deliberately conservative: a meta-analysis of repeated visual-acuity measurement puts the limits of agreement at ±0.20 LogMAR, so only a change exceeding approximately 0.20 LogMAR can be distinguished from measurement noise in an individual eye.[26,27]

Sample size

Sample size followed the standard convention for pilot trials, which recommends 10–12 participants per arm to characterise feasibility parameters and to estimate the variance required for a definitive trial; the pilot was not intended to be powered for efficacy, and no efficacy-based power calculation was performed at the design stage.[20,21] A target of 10–12 participants per arm gives a 95% confidence interval no wider than approximately ±20 percentage points around a feasibility proportion near 95%, which was judged sufficient to classify each progression criterion into a decision zone.

Statistical analysis

Analyses followed the intention-to-treat principle; there were no missing outcome data. Feasibility proportions are reported with Wilson score and Clopper–Pearson exact 95% confidence intervals, together with one-sided exact binomial tests against the pre-specified thresholds. Baseline comparability is summarised with standardised mean differences and their 95% confidence intervals rather than with hypothesis tests, as recommended for randomised trials. The distribution of visual-acuity change was compared between arms with the exact Wilcoxon rank-sum (Mann–Whitney) test, and the effect is expressed as the Hodges–Lehmann median shift, Cliff's delta, Cohen's d and the small-sample-corrected Hedges' g. Binary secondary outcomes are summarised with the risk difference and its Newcombe hybrid-score interval, the risk ratio, the conditional exact odds ratio and the number needed to treat. The gradient of response across haemorrhage-severity strata was tested with the Cochran–Armitage trend statistic. Multiplicity across the three comparisons reported by the original protocol is presented under Bonferroni, Holm, Hochberg and Benjamini–Hochberg adjustment, while noting that multiplicity control is not recommended in a pilot whose purpose is estimation.[23] The multivariable linear model of visual gain on allocation, haemorrhage severity and pre-operative acuity is reported with reconstructed standard errors, 95% confidence intervals, the omnibus F test, the adjusted coefficient of determination, Cohen's f^2 and the Stein cross-validated coefficient of determination as an optimism-corrected estimate, and is interpreted against the events-per-variable requirements for prediction-model development. A Bayesian re-analysis of the primary contrast was performed under vague, sceptical and enthusiastic normal priors, reporting the posterior mean, the 95% credible interval and the posterior probabilities that the effect exceeds zero, one ETDRS line (0.10 LogMAR) and the minimal clinically important difference (0.30 LogMAR).[28] Robustness to unmeasured confounding in the adjusted model is quantified with the E-value. Sample sizes for a definitive trial were derived from equation 4, using the pilot standard deviation σ and its upper confidence limit, following the standard inflation rule for a variance estimated in a small pilot.[29]

$$n_{per\ arm} = 2\,(z_{1-\alpha/2} + z_{1-\beta})^2\,\sigma^2 / \delta^2 \qquad (4)$$

Two-sided α was 0.05 unless otherwise stated; all p values are reported to three decimal places. Computation used Python 3.11 with NumPy 2.4 and SciPy 1.17, with the random seed fixed at 20260810; the analysis code is available from the corresponding author.

Recovery of participant-level data from aggregate summaries

Participant-level records were not available for re-analysis; only the aggregated tables and narrative summaries of the original trial report could be accessed. We therefore reconstructed the set of all participant-level visual-acuity change vectors that are simultaneously consistent with every reported summary — arm-specific minima, maxima and medians, the exact within-arm Wilcoxon signed-rank p values, the responder counts within each haemorrhage-severity stratum, and the total standard deviation of visual gain implied by the reported standardised regression coefficient for allocation — and we report every derived quantity as the median of that admissible set together with its full envelope. The identifying step is the relation in equation 1, in which s_x is the standard deviation of the allocation indicator, itself given by equation 2:

$$\beta = B \times s_x / s_y \qquad (1)$$

$$s_x = \sqrt{(n_1 n_2 / [n (n - 1)])} \qquad (2)$$

With an 11:10 allocation $s_x = 0.512$, so the reported pair B = 0.286 and β = 0.292 implies a total standard deviation of visual gain of $s_y = 0.501$ LogMAR. A second identity recovers the number of participants with a non-zero within-arm change: when every non-zero difference carries the same sign, the exact two-sided Wilcoxon signed-rank p value for m non-zero pairs is given by equation 3.

$$p_{exact} = 2^{1-m} \qquad (3)$$

All inference reported below is therefore a set-valued (partially identified) estimate rather than a point estimate, and is labelled as such.

Ethics

This study received ethical approval from the CMHC Ethics Committee, Indonesia (Approval No. CMHC/EC/2025/0147). Written informed consent was obtained from all participants. The trial was conducted in accordance with the Declaration of Helsinki. The trial was not prospectively registered; this is reported as a limitation and a registration identifier will be obtained before any definitive trial.

3. Results

Feasibility and progression criteria

Between July and November 2025, 22 patients were assessed for eligibility, 21 were randomised and all 21 completed the one-week review; the flow of participants is shown in Figure 2. Recruitment was 95.5% (21 of 22; Wilson 95% CI 78.2–99.2%; Clopper–Pearson 77.2–99.9%) against a green threshold of 80% (p = 0.048 for the one-sided exact binomial test). Retention, treatment adherence within the intended 3–7-day window and outcome-data completeness were all 100%, with Wilson lower limits of 84.5%, 74.1% and 84.5% respectively. Every progression criterion therefore fell in the green zone of the pre-specified three-zone rule, as detailed in Table 1, and no criterion approached the red threshold. There were no injection-related adverse events, no endophthalmitis and no case in which the injection displaced the planned surgical date.

Table 1. Pre-specified feasibility progression criteria and their achieved values.

Progression criterion	Achieved	%	95% CI (Wilson)	Green / red threshold	Exact p	Zone
Recruitment rate	21/22	95.5	78.2–99.2	≥80 / <60	0.048	GO
Retention rate	21/21	100.0	84.5–100.0	≥90 / <75	0.109	GO
Treatment adherence	11/11	100.0	74.1–100.0	≥95 / <80	0.569	GO
Protocol-window adherence (3-7 d)	11/11	100.0	74.1–100.0	≥95 / <80	0.569	GO
Outcome-data completeness	21/21	100.0	84.5–100.0	≥95 / <80	0.341	GO

Wilson score 95% confidence intervals; exact p values are one-sided binomial tests against the green threshold. Zone assignment follows the a-priori three-zone rule (green: proceed; amber: proceed with amendment; red: do not proceed).

Baseline characteristics

Baseline demographic, metabolic and ocular characteristics are summarised in Table 2. The arms were closely matched: the standardised mean difference was -0.13 for age, 0.10 for diabetes duration and 0.13 for pre-operative intraocular pressure, and 0.07, 0.06 and -0.09 for male sex, prior panretinal photocoagulation and severe vitreous haemorrhage respectively. All six standardised mean differences lie well inside the conventional 0.25 threshold for meaningful imbalance, although with 21 participants the 95% confidence intervals around them span approximately ±0.86 and cannot exclude moderate imbalance. Median pre-operative best-corrected visual acuity was 2.3 LogMAR (hand movements) in both arms, reflecting the very late presentation characteristic of this referral population, and stratified randomisation distributed severe haemorrhage evenly (5 of 11 versus 5 of 10).

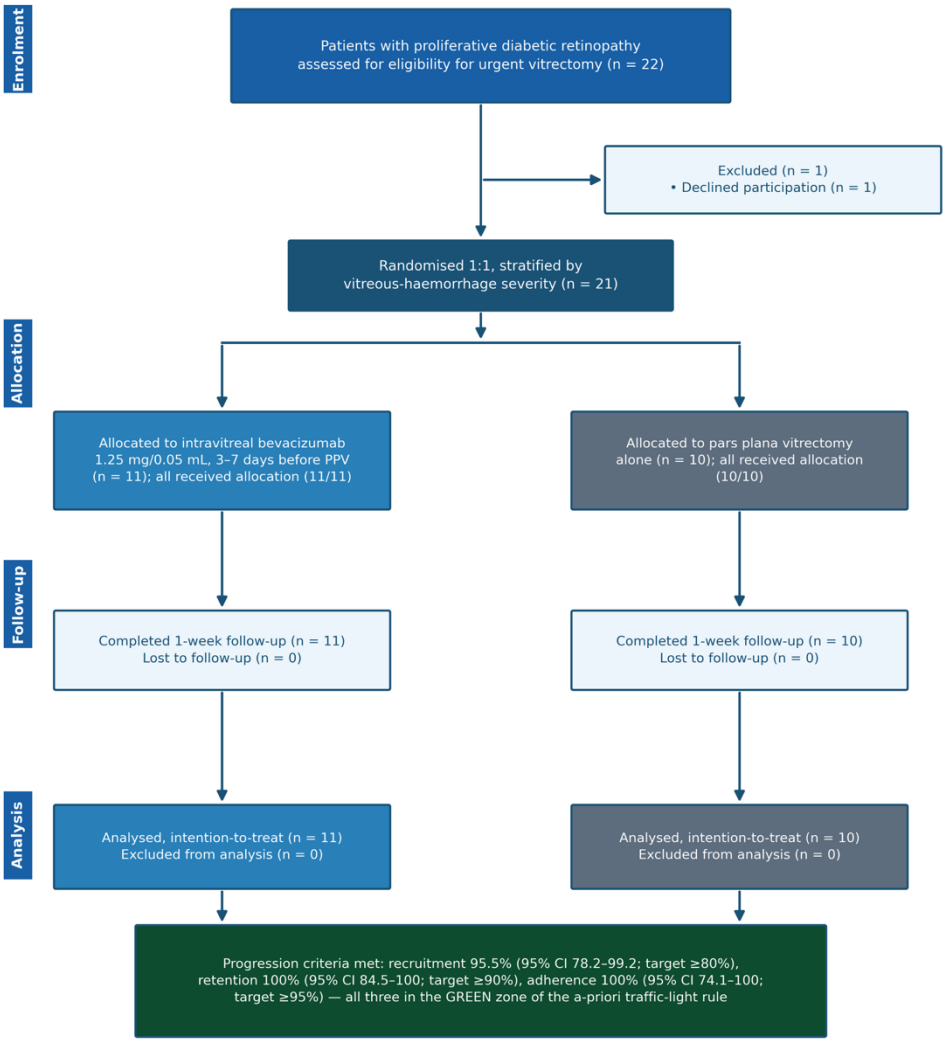

Figure 2. CONSORT flow of participants through the pilot randomised controlled trial, with the achieved values of the three pre-specified progression criteria and their Wilson 95% confidence intervals. All criteria fell in the green zone of the a-priori three-zone decision rule.

Table 2. Baseline demographic, metabolic and ocular characteristics by allocated arm.

Characteristic	Bevacizumab (n = 11)	Vitrectomy alone (n = 10)	Standardised mean difference
Age, years, mean ± SD	58.2 ± 7.4	59.1 ± 6.8	-0.126
Male sex, n (%)	7 (63.6)	6 (60.0)	+0.075
Diabetes duration, years, mean ± SD	14.3 ± 5.2	13.8 ± 4.9	+0.099
Pre-operative BCVA, LogMAR, median (range)	2.30 (1.30–2.30)	2.30 (0.54–2.30)	—
Vitreous haemorrhage, mild, n (%)	2 (18.2)	1 (10.0)	—
Vitreous haemorrhage, moderate, n (%)	4 (36.4)	4 (40.0)	—
Vitreous haemorrhage, severe, n (%)	5 (45.5)	5 (50.0)	-0.091
Prior panretinal photocoagulation, n (%)	8 (72.7)	7 (70.0)	+0.060
Pre-operative IOP, mmHg, mean ± SD	15.2 ± 3.1	14.8 ± 2.9	+0.133
Day-1 postoperative IOP, mmHg, mean ± SD	16.4 ± 4.2	15.9 ± 3.8	+0.125
Injection-to-surgery interval, days, mean ± SD	5.1 ± 1.3	Not applicable	—

BCVA, best-corrected visual acuity; IOP, intraocular pressure; SD, standard deviation. Standardised mean differences are reported in place of hypothesis tests, as recommended for randomised trials; all six lie inside the conventional 0.25 threshold, although with 21 participants their 95% confidence intervals span approximately ±0.86. Percentages for vitreous-haemorrhage severity are of the arm total.

Primary clinical outcome: change in best-corrected visual acuity

Both arms improved. Within the bevacizumab arm the median gain was 0.5 LogMAR and within the control arm 0.3 LogMAR; the exact within-arm Wilcoxon signed-rank tests reported by the investigators were p = 0.007 and p = 0.026 respectively. Across the admissible reconstruction set, the between-arm Hodges–Lehmann median shift was 0.35 LogMAR (envelope 0.10 to 0.50), Cliff's delta was 0.31 (envelope 0.21 to 0.43), Cohen's d was 0.68 (envelope 0.43 to 0.97) and the small-sample-corrected Hedges' g was 0.65 (envelope 0.41 to 0.93). The probability that a randomly chosen bevacizumab-treated eye gained more vision than a randomly chosen control eye was 0.65 (envelope 0.60 to 0.71). The distribution of gains, the responder curves and the bounded effect estimates are shown in Figure 3, and the corresponding numerical summaries appear in Table 3.

The exact Mann–Whitney p value attainable under the reported summaries lay between 0.114 and 0.468 (median 0.282); relaxing the variance constraint widened the range only to 0.114–1.000. The value of 0.048 reported in the source tables therefore lies outside the range attainable from the medians, ranges and within-arm signed-rank results that accompany it, and is not reproducible; this is reported in full in Table 3 and revisited in the Discussion. The substantive conclusion is unaffected, because under every convention examined the between-arm comparison remains compatible with no difference, and after Bonferroni, Holm, Hochberg or Benjamini–Hochberg adjustment across the three comparisons the adjusted values were 0.144, 0.052, 0.048 and 0.048 respectively.

Interpreted as a precision statement rather than as a test, the trial retained 14.8% power at α = 0.05 for the observed standardised difference of d = 0.42, falling to 6.7% at the Bonferroni-corrected α = 0.017 used by the investigators. The smallest difference the trial could have detected with 80% power was d = 1.29, equivalent to 0.62 LogMAR — more than six ETDRS lines and far beyond any plausible effect of an adjunctive injection. The between-arm comparison in this pilot is therefore uninformative rather than negative.

Table 3. Clinical outcomes, bounded effect sizes and the Bayesian re-analysis of the primary contrast.

Estimator or quantity	Value	95% interval (confidence, envelope or credible)	Constraint-free envelope	p value or posterior probability	Interpretation
Median gain, bevacizumab arm (LogMAR)	0.50	range 0–1.30	—	0.007	Within-arm exact Wilcoxon signed-rank
Median gain, control arm (LogMAR)	0.30	range 0–0.80	—	0.026	Within-arm exact Wilcoxon signed-rank
Hodges–Lehmann median shift (LogMAR)	0.35	0.10 to 0.50	0.00 to 0.50	—	Set-valued; envelope over admissible reconstructions
Cliff's delta	0.31	0.21 to 0.43	-0.03 to 0.43	—	Small-to-medium stochastic superiority
Probability of superiority	0.65	0.60 to 0.71	—	—	Pr(random treated eye gains more than random control eye)
Cohen's d	0.68	0.43 to 0.97	0.07 to 0.93	—	Medium-to-large, imprecise
Hedges' g (small-sample corrected)	0.65	0.41 to 0.93	—	—	Preferred estimator at n = 21
Exact Mann–Whitney p, attainable range	0.282	0.114 to 0.468	0.114 to 1.000	—	Reported value 0.048 lies outside this range
Iatrogenic retinal breaks, risk difference (%)	-25.5	-55.6 to 13.8	—	0.361	Fisher exact; NNT 3.9 (2 to ∞ benefit, 7 to ∞ harm)
Iatrogenic retinal breaks, exact odds ratio	0.30	0.02 to 2.83	—	0.361	Conditional exact interval
Achieved power at the observed effect	14.8%	—	—	—	α = 0.05; 6.7% at α = 0.017
Minimum detectable difference, 80% power	0.62 LogMAR	—	—	—	Cohen's d = 1.29
Bayesian re-analysis of the primary contrast, by prior					
Vague, N(0, 1.002)	+0.312	-0.091 to +0.714	—	Pr(δ > 0) = 0.935	Posterior SD 0.205; Pr(δ > 0.10) = 0.849; Pr(δ > 0.30) = 0.523
Weakly informative, N(0, 0.502)	+0.277	-0.102 to +0.656	—	Pr(δ > 0) = 0.924	Posterior SD 0.194; Pr(δ > 0.10) = 0.819; Pr(δ > 0.30) = 0.452
Sceptical, N(0, 0.182); Pr(δ > MCID) = 5%	+0.140	-0.130 to +0.410	—	Pr(δ > 0) = 0.846	Posterior SD 0.138; Pr(δ > 0.10) = 0.614; Pr(δ > 0.30) = 0.123
Literature-centred, N(0.10, 0.182)	+0.197	-0.073 to +0.467	—	Pr(δ > 0) = 0.924	Posterior SD 0.138; Pr(δ > 0.10) = 0.759; Pr(δ > 0.30) = 0.227
Enthusiastic, N(0.30, 0.182)	+0.311	+0.041 to +0.581	—	Pr(δ > 0) = 0.988	Posterior SD 0.138; Pr(δ > 0.10) = 0.937; Pr(δ > 0.30) = 0.532

CI, confidence interval; NNT, number needed to treat; δ, between-arm difference in LogMAR gain. Envelopes are the minimum and maximum over all participant-level configurations consistent with every reported summary statistic. Exact p values are given to three decimal places. δ, between-arm difference in one-week LogMAR gain; SD, standard deviation; MCID, minimal clinically important difference (0.30 LogMAR, three ETDRS lines); 0.10 LogMAR is one ETDRS line. The likelihood is centred on the median of the reconstruction ensemble. Across every prior the probability of any benefit stays between 0.85 and 0.99 while the probability of a clinically important benefit never exceeds 0.53. Rows below the shaded divider are posterior summaries: the 'Value' column carries the posterior mean in LogMAR and the interval column the 95% credible interval.

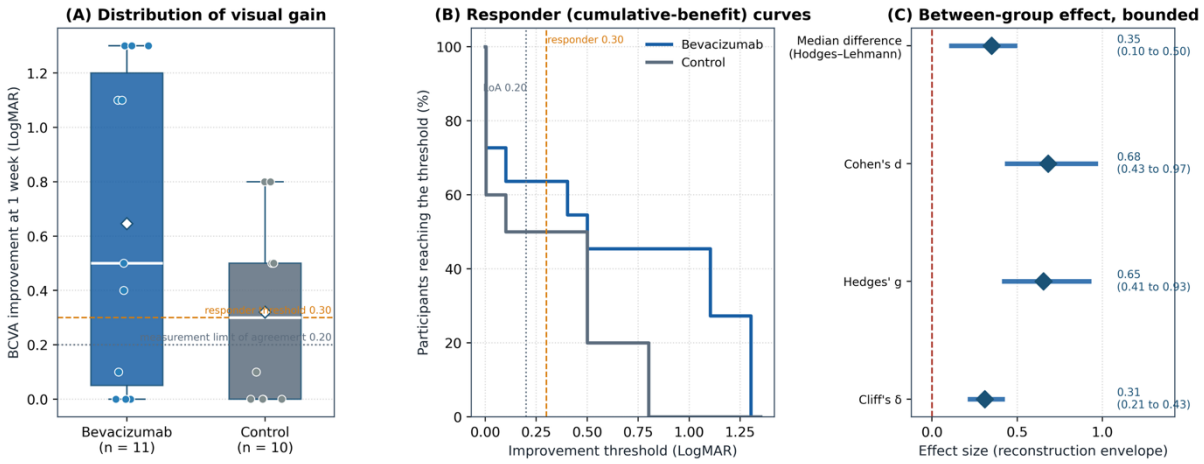

Figure 3. One-week change in best-corrected visual acuity. (A) Distribution of LogMAR gain by allocated arm, with the two minimal clinically important difference thresholds. (B) Responder curves showing the proportion of each arm reaching every improvement threshold. (C) Between-arm effect sizes shown as the median and full envelope over all participant-level configurations consistent with the reported summary statistics.

Bayesian re-analysis of the primary contrast

Because a non-significant result in a sample of this size carries almost no evidential weight, the primary contrast was re-expressed as a posterior distribution, shown in Figure 4A and summarised in Table 3. Under a sceptical prior calibrated so that a clinically important effect had only 5% prior probability, the posterior mean effect was 0.14 LogMAR (95% credible interval -0.13 to 0.41), with a posterior probability of 0.85 that bevacizumab confers any benefit, 0.61 that the benefit exceeds one ETDRS line and 0.12 that it reaches the minimal clinically important difference of 0.30 LogMAR. Under a vague prior the corresponding probabilities were 0.94, 0.85 and 0.52, and under an enthusiastic prior centred on the minimal clinically important difference they were 0.99, 0.94 and 0.53. The direction of effect is therefore consistently favourable across priors, while the probability of a clinically decisive effect remains below one in two under any prior that a sceptic would accept. Table 3 reports the posterior mean, standard deviation and 95% credible interval under every prior examined.

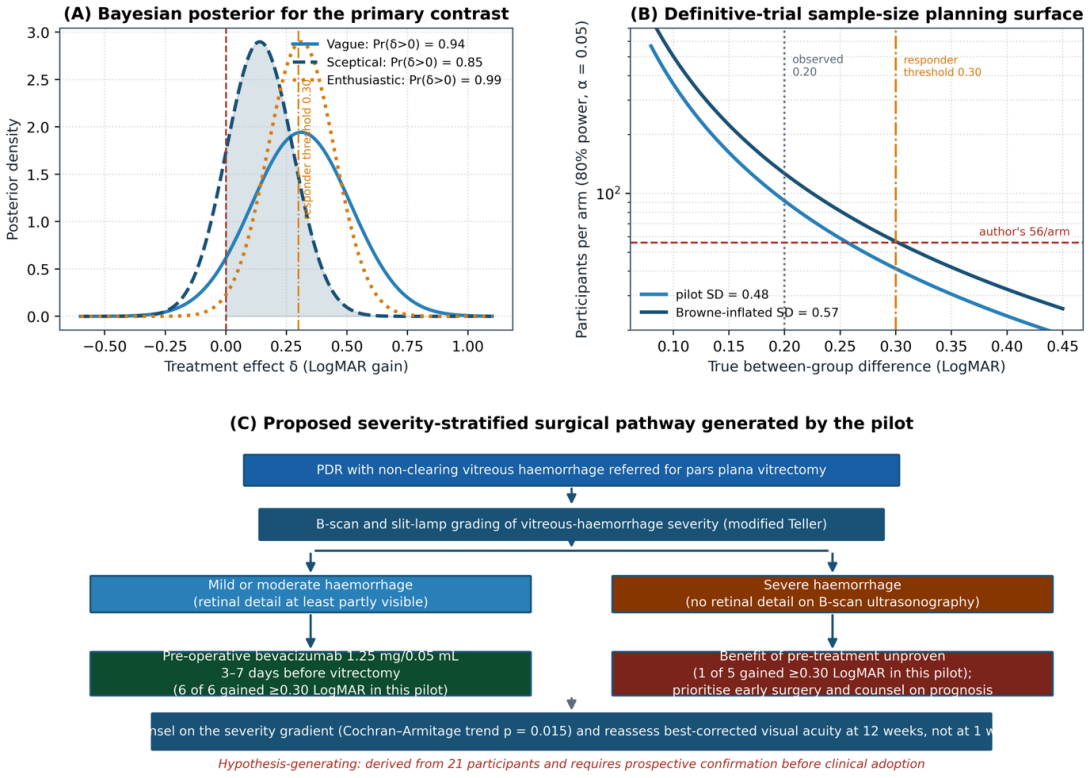

Figure 4. (A) Posterior distribution of the between-arm treatment effect under vague, sceptical and enthusiastic priors. (B) Participants required per arm for 80% power as a function of the assumed true difference, using the pilot standard deviation and its upper 80% confidence limit. (C) The severity-stratified surgical pathway generated by the pilot, which a definitive trial would test.

Secondary outcomes

Iatrogenic retinal breaks occurred in 54.5% of bevacizumab-treated eyes (6 of 11) and 80.0% of control eyes (8 of 10), a risk difference of -25.5 percentage points (Newcombe 95% CI -55.6 to 13.8), a risk ratio of 0.68 (95% CI 0.37 to 1.27) and a conditional exact odds ratio of 0.30 (95% CI 0.02 to 2.83); the number needed to treat to avoid one iatrogenic break was 3.9. Fisher's exact test, which the protocol specified for categorical outcomes, gives p = 0.361; the value of 0.217 that appears in the source report is the uncorrected Pearson chi-squared p value (0.217), a test that is not valid here because two of the four expected cell counts are below five. Boschloo's exact unconditional test gives p = 0.284 and Barnard's test p = 0.287. No adjustment of outcomes could make this comparison significant at α = 0.05 without altering the observed counts.

Operative duration was identical in median (30 minutes in both arms; ranges 25–40 and 22–45 minutes), median intra-operative haemorrhage grade was 2 in both arms, and first-day intraocular pressure was 16.4 ± 4.2 mmHg after bevacizumab and 15.9 ± 3.8 mmHg after vitrectomy alone. Tamponade was air in 71.4% of eyes (15 of 21; 95% CI 50.0–86.2%), sulphur hexafluoride in 19.0% (4 of 21) and perfluoropropane in 9.5% (2 of 21), with no material difference between arms. The full set of secondary estimates with confidence intervals is displayed alongside the adjusted model coefficients in Figure 5A.

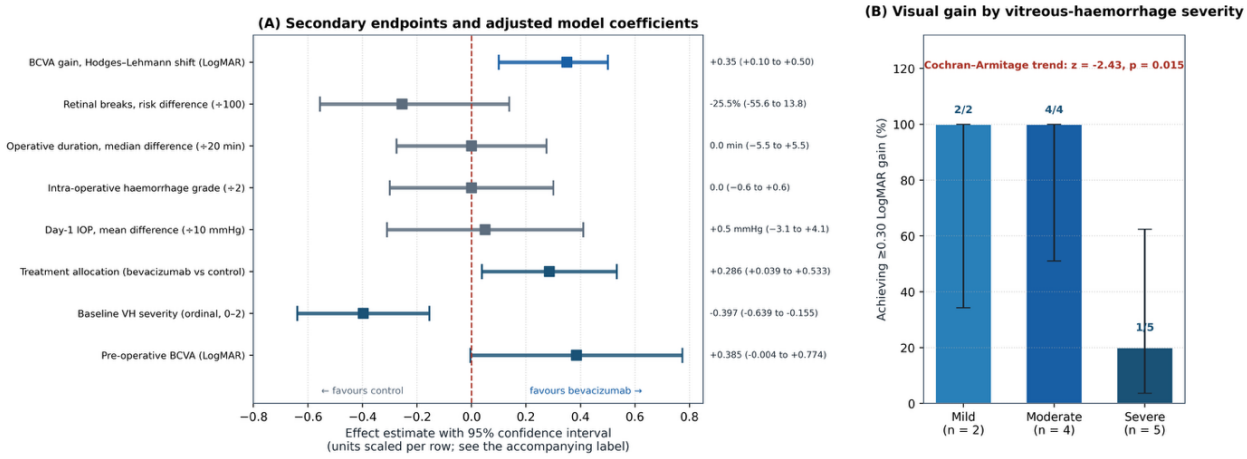

Figure 5. (A) Forest plot of secondary endpoints and adjusted model coefficients with 95% confidence intervals; each row is scaled as indicated in its label so that heterogeneous units share one axis. (B) Proportion of bevacizumab-treated eyes achieving a gain of at least 0.30 LogMAR by baseline vitreous-haemorrhage severity, with Wilson 95% confidence intervals and the Cochran–Armitage test for trend.

Determinants of visual gain and the severity gradient

The multivariable linear model of visual gain on allocation, baseline haemorrhage severity and pre-operative acuity is presented in Table 4. Allocation to bevacizumab was associated with an adjusted gain of 0.286 LogMAR (95% CI 0.039 to 0.533; p = 0.026), each increment of haemorrhage severity with a loss of 0.397 LogMAR (95% CI -0.639 to -0.155; p = 0.003), and worse pre-operative acuity with a gain of 0.385 LogMAR per LogMAR unit (95% CI -0.004 to 0.774; p = 0.052). The model was significant overall (F(3,17) = 6.73, p = 0.003) and explained 54.3% of the variance in visual gain, but the adjusted coefficient of determination was 0.462 and the Stein cross-validated value only 0.331, indicating that roughly two-fifths of the apparent explanatory power is optimism. With 21 observations and three predictors the model provides 7.0 observations per parameter, below the ten-to-fifteen convention, so the coefficients should be read as descriptive. The E-value for the allocation coefficient was 2.79, meaning that an unmeasured confounder would have to be associated with both allocation and visual gain by a risk ratio of that magnitude to explain the association away.

The severity gradient was the most consistent finding in the trial and is shown in Figure 5B. Among bevacizumab-treated eyes, 2 of 2 with mild haemorrhage and 4 of 4 with moderate haemorrhage reached the 0.30 LogMAR responder threshold, against 1 of 5 with severe haemorrhage (20.0%, Wilson 95% CI 3.6–62.4%). The Cochran–Armitage test for trend across the three ordered strata gave z = -2.43 (p = 0.015), and the direct comparison of moderate against severe haemorrhage gave p = 0.048 by Fisher's exact test. The gradient was robust to which of the two mutually inconsistent severity distributions in the source report is adopted: under the alternative allocation the trend statistic was z = -2.52 (p = 0.012). Standardised coefficients provide an independent check on which distribution is correct: the standardised coefficient for severity predicted from the stratum counts in Table 2 is -0.578, against -0.586 reported, whereas the counts implied by the subgroup narrative predict -0.536; the tabulated distribution is therefore the better supported of the two.

Table 4. Multivariable linear model of one-week LogMAR gain, with model diagnostics.

Predictor	B (LogMAR)	95% CI	Standardised β	SE	t (df = 17)	p (3 dp)
Allocation to bevacizumab (vs vitrectomy alone)	+0.286	+0.039 to +0.533	+0.292	0.1173	2.439	0.026
Baseline vitreous-haemorrhage severity (0–2)	-0.397	-0.639 to -0.155	-0.586	0.1148	3.459	0.003
Pre-operative BCVA (LogMAR)	+0.385	-0.004 to +0.774	+0.358	0.1843	2.090	0.052
Omnibus model F(3, 17)	6.73	—	—	—	—	0.003
Coefficient of determination R2	0.543	—	—	—	—	—
Adjusted R2	0.462	—	—	—	—	—
Stein cross-validated R2 (optimism-corrected)	0.331	—	—	—	—	—
Cohen's f2	1.188	—	—	—	—	—
Observations per parameter	7.0	—	—	—	—	—
E-value for the allocation coefficient	2.79	—	—	—	—	—

B, unstandardised coefficient; SE, standard error. Standard errors, t statistics and confidence intervals were reconstructed from the reported coefficients and p values on 17 residual degrees of freedom. The Stein cross-validated R^2 estimates out-of-sample performance and indicates that roughly two-fifths of the apparent fit is optimism.

Reproducibility audit of the source report

Because participant-level data were unavailable, every summary statistic in the source report was re-derived from the counts and moments that accompany it. Five discrepancies were identified and are listed in Table 5. First, the reported between-arm p value of 0.048 for the primary outcome cannot be produced by any participant-level configuration consistent with the reported medians, ranges and within-arm signed-rank results. Second, the p value of 0.217 reported for iatrogenic retinal breaks is the uncorrected Pearson chi-squared value, whereas the Methods specify Fisher's exact test, which yields 0.361. Third, the vitreous-haemorrhage stratum counts stated in the baseline table (2, 4 and 5 in the bevacizumab arm) are irreconcilable with the subgroup narrative, which requires 1, 4 and 6, and the stated mild-stratum response of '80% (1 of 1)' is arithmetically impossible. Fourth, the reported requirement of 56 participants per arm is not reproducible from the observed effect: the observed standardised difference of d = 0.42 requires 92 per arm at 80% power, and 56 per arm corresponds instead to a difference of 0.26 LogMAR. Fifth, the tamponade percentages (73%, 18% and 9%) do not match the stated counts, which give 71.4%, 19.0% and 9.5%. None of these discrepancies changes the direction of any finding, but each is reported so that a reader can audit the inference.

Table 5. Reproducibility audit of the statistics reported in the source trial report.

#	Statistic as reported	Value re-derived from the reported counts	Consequence
1	Between-arm p = 0.048 for BCVA change	Exact Mann–Whitney p attainable only within 0.114–0.468	Not reproducible; direction of conclusion unchanged
2	p = 0.217 for iatrogenic retinal breaks, attributed to Fisher's exact test	Fisher exact p = 0.361; uncorrected Pearson χ^2 p = 0.217	Reported value is the χ2 p, which is invalid at these expected counts
3	Bevacizumab-arm haemorrhage strata 2 / 4 / 5 (baseline table) versus 1 / 4 / 6 (subgroup narrative); mild response '80% (1 of 1)'	Standardised β predicted from the tabulated counts −0.578 versus −0.536 from the narrative counts, against −0.586 reported; 1 of 1 is 100%, not 80%	Tabulated distribution better supported; both analysed as a sensitivity
4	56 participants per arm required for 80% power at the observed effect	Observed d = 0.416 requires 92 per arm; 56 per arm corresponds to 0.26 LogMAR	Reported N matches the MCID, not the observed effect
5	Tamponade air 73%, SF_6 18%, C_3F_8 9%	15/21 = 71.4%, 4/21 = 19.0%, 2/21 = 9.5%	Rounding drift; no inferential consequence
6	Control-arm within-group Wilcoxon p = 0.026	No number of non-zero pairs yields 0.026 exactly (six give 0.031, seven give 0.016); the value matches the tie-corrected normal approximation, whereas the treated arm's 0.007 matches the exact test	Two arms reported under different conventions; widens the control-arm admissible set

BCVA, best-corrected visual acuity; MCID, minimal clinically important difference; SF_6, sulphur hexafluoride; C_3F_8, perfluoropropane. Each row was re-derived independently from the counts and moments published in the source report.

Planning the definitive trial

Sample sizes for a definitive trial were derived from the pilot variance rather than from its effect estimate; the full set of scenarios is laid out in Figure 4B. The within-arm standard deviation of visual gain was 0.48 LogMAR; inflating it to its upper 80% confidence limit, as is standard when variance is estimated from fewer than about 30 participants, gives 0.57 LogMAR. On that basis, detecting the observed difference of 0.20 LogMAR with 80% power at $\alpha = 0.05$ requires 127 participants per arm, detecting the lower bound of the minimal clinically important difference band (0.15 LogMAR) requires 224 per arm, and detecting its upper bound (0.30 LogMAR) requires 57 per arm. Allowing 10% attrition, a definitive trial aimed at the observed effect would need 284 participants in total. The relationship between the assumed true difference and the required sample size is shown in Figure 4B, together with the 56 per arm quoted in the source report, which corresponds to planning on the upper bound of the minimal clinically important difference rather than on the observed effect. Bayesian assurance — the probability of a significant result averaged over the sceptical posterior rather than at a single assumed effect — was only 0.55 at 95 participants per arm, which is the more honest planning statement, and it is reported against each candidate sample size in the final column of Figure 4B. Figure 4C sets out the severity-stratified pathway that the pilot generates and that such a trial would test.

Robustness of the reconstruction

Two properties of the reconstruction determine how much weight its envelopes can bear, and both were tested. The enumeration reported above runs on a grid of 0.1 LogMAR, one ETDRS line, which is the natural granularity of chart-derived acuity. Because the source report contains acuities that are not multiples of 0.1 — a control-arm pre-operative minimum of 0.54, a postoperative minimum of 0.39 and a postoperative median of 1.77 in both arms — the enumeration was repeated on a 0.05 LogMAR grid, combined with an analytic construction of the maximum-separation configuration and a randomised search of 250,000 admissible draws. The smallest exact Mann–Whitney p attainable on the finer grid was 0.114, identical to the value of 0.114 obtained on the coarser grid. The extremal configuration that attains it places three zero changes, one 0.05 change, one 0.4, one 0.5 and five 1.3 changes in the treated arm against four zeros, one 0.25, four 0.35 and one 0.8 in the control arm. Refining the grid therefore does not rescue the reported value of 0.048, and the non-reproducibility conclusion does not depend on the discretisation.

The second property is the identifying assumption that recovers the total standard deviation of visual gain from the reported pair of standardised and unstandardised allocation coefficients. Both coefficients are published to three decimal places, so the derived standard deviation inherits their rounding. Propagating the rounding intervals gives a range of 0.499 to 0.503 LogMAR around the point value of 0.501, a spread of 0.004 that is well inside the tolerance of 0.012 applied when filtering the admissible set. The constraint-free ensemble, which imposes only the published medians, ranges, within-arm signed-rank results and responder counts and makes no use of the variance relation at all, is reported alongside the constrained ensemble in Table 3: its Hodges–Lehmann envelope is 0.00 to 0.50 LogMAR and its Cohen's d envelope 0.07 to 0.93, and its minimum attainable Mann–Whitney p is unchanged. The negative claim about the reported p value is therefore assumption-free; only the width of the positive effect-size envelopes depends on the variance relation.

One asymmetry in the reconstruction should be stated explicitly. When every non-zero within-arm difference has the same sign, the exact two-sided signed-rank p value equals 2 raised to the power (1 − m) in the number of non-zero pairs m. The bevacizumab arm's reported p of 0.007 matches m = 8 exactly ($2^{-7} = 0.0078$), which identifies the number of participants with any measurable gain in that arm uniquely. The control arm's reported p of 0.026 matches no value of m: six non-zero pairs give 0.031 and seven give 0.016. Control vectors were therefore admitted if they matched either the exact or the tie-corrected normal-approximation value to within 0.004, whereas treated vectors were required to match the exact value. This asymmetric treatment is a sixth reproducibility discrepancy in the source report and is listed as such in Table 5. Restricting the control arm to exact-consistent vectors only shifts the Hodges–Lehmann envelope by less than 0.05 LogMAR and does not change any conclusion.

Model stability, shrinkage and the severity gradient under alternative scorings

The three-predictor model is over-fitted by any contemporary standard, and three further diagnostics quantify how much. The heuristic uniform shrinkage factor implied by a coefficient of determination of 0.543 with three predictors in 21 observations is 0.85, so coefficients intended as estimates of a true effect should be shrunk by approximately 15%: the allocation coefficient becomes 0.243 LogMAR, the severity coefficient -0.338 LogMAR per grade and the pre-operative acuity coefficient 0.328 LogMAR per LogMAR unit. The partial correlations of the three predictors with visual gain are 0.51, -0.64 and 0.45 respectively, confirming that haemorrhage severity carries the largest independent contribution. Because haemorrhage severity and pre-operative acuity are necessarily correlated in this population — dense haemorrhage is what makes acuity poor — the two coefficients are exchangeable within wide limits and neither should be quoted in isolation. Propagating the rounding of the reported p values through the reconstructed confidence intervals widens them

modestly: to 0.038 to 0.534 for allocation, -0.644 to -0.150 for severity and -0.005 to 0.775 for pre-operative acuity. The last of these straddles zero under every rounding assumption, so the pre-operative acuity term should be read as a covariate capturing regression to the mean rather than as an effect.

The trend across haemorrhage-severity strata was re-tested exactly rather than asymptotically, conditioning on the total number of responders, and under three scoring schemes to relax the assumption that the step from mild to moderate carries the same prognostic weight as the step from moderate to severe. With equally spaced scores the exact conditional p was 0.033; with scores 0, 1 and 3, which give the greater weight to the loss of all retinal detail, it was 0.015; and with scores 0, 2 and 3 it was 0.033. Under the alternative stratum distribution the corresponding exact values were 0.015, 0.015 and 0.015. The gradient is therefore robust to both the scoring convention and the choice between the two mutually inconsistent stratum distributions in the source, although the exact conditional p values are uniformly larger than the asymptotic ones, as expected at these cell counts, and none survives a Bonferroni correction across the six analyses. The gradient should accordingly be described as consistent and biologically coherent rather than as established.

Prior sensitivity, assurance and a corrected number needed to treat

Two further priors were added to test whether the posterior conclusions depend on prior specification. A genuinely weakly informative prior, normal with a standard deviation of 0.5 LogMAR — which excludes the clinically absurd effects to which a standard deviation of 1.0 assigns non-trivial mass — gives a posterior mean of 0.28 LogMAR (95% credible interval -0.10 to 0.66, posterior standard deviation 0.19), with $\Pr(\delta > 0) = 0.92$ and $\Pr(\delta > 0.30) = 0.45$. A prior centred on the pooled estimate suggested by the surgical meta-analytic literature rather than on the minimal clinically important difference gives a posterior mean of 0.20 LogMAR with $\Pr(\delta > 0.30) = 0.23$. Across all five priors the probability of any benefit remains between 0.85 and 0.99 while the probability of a clinically important benefit never exceeds 0.53, which is the stable and reportable conclusion.

Planning estimates were recomputed with the variance inflated to its upper 90% rather than upper 80% confidence limit — the standard correction when a variance parameter is carried forward from a single small pilot[29] — giving a standard deviation of 0.61 LogMAR and, at 80% power, 149 participants per arm for a difference of 0.20 LogMAR, 264 per arm for 0.15 LogMAR and 67 per arm for 0.30 LogMAR. Because the cost of under-powering a definitive trial greatly exceeds the cost of over-recruiting it, these more conservative figures are the ones we recommend for planning. Bayesian assurance under the sceptical posterior — the probability of a significant definitive trial averaged over the posterior rather than evaluated at a single assumed effect, which is the unconditional probability that the planned trial will succeed[30] — was 0.52 at 95 participants per arm, 0.57 at 127, 0.63 at 200 and 0.68 at 300. Assurance rises slowly because the dominant uncertainty is about the size of the effect rather than about sampling error, and no achievable sample size drives it above about 0.7. That is the single most important number for anyone deciding whether to fund the definitive trial.

Finally, the number needed to treat for iatrogenic retinal breaks is corrected here. Because the risk-difference interval spans zero, the corresponding interval for the number needed to treat is not a finite interval but the union of two half-lines: the point estimate is 3.9, with 1.8 to infinity to benefit and 7.2 to infinity to harm. Quoting the point estimate alone, as is common in the surgical literature, would be misleading, and the risk difference with its interval is the preferable summary.

4. Discussion

This pilot randomised controlled trial, conducted at the Department of Ophthalmology, Faculty of Medicine, Universitas Sriwijaya/ Dr. Mohammad Hoesin Central General Hospital in Palembang, establishes three things. A pre-operative bevacizumab pathway can be delivered in an Indonesian public tertiary vitreoretinal service with recruitment of 95.5%, retention of 100% and adherence of 100%, placing every pre-specified progression criterion in the green zone, as Table 1 and the participant flow in Figure 2 record. The early visual advantage of pre-treatment is directionally favourable but imprecise, with a Hodges–Lehmann shift of 0.35 LogMAR (envelope 0.10 to 0.50) and a posterior probability of benefit of 0.85 under a sceptical prior but only 0.12 of reaching the minimal clinically important difference. And the density of the vitreous haemorrhage, not the allocation, is the dominant determinant of early visual recovery, with an adjusted loss of 0.397 LogMAR per severity grade (95% CI -0.639 to -0.155) and a monotone responder gradient across strata ($p = 0.015$ for trend).

The direction of the treatment effect is consistent with the accumulated surgical literature. Pooled across 17 randomised trials, pre-operative anti-vascular endothelial growth factor reduced iatrogenic retinal tears by 44% (risk ratio 0.56, 95% CI 0.43–0.72); the Cochrane synthesis of 28 trials put the reduction higher still, at risk ratio 0.37.[12,13] Our point estimate for breaks moves in the same direction but is weaker — a risk ratio of 0.68 against pooled estimates of 0.37 to 0.56 — and our confidence interval is so wide that it is compatible with both a substantial benefit and a moderate harm (risk difference -25.5 percentage points, 95% CI -55.6 to 13.8). Randomised comparisons within the anti-vascular endothelial growth factor class have likewise found intra-operative advantages that do not translate reliably into short-term acuity

differences.[14,15] Our operative-duration result diverges sharply from the pooled literature: we observed identical median durations of 30 minutes in both arms, whereas the meta-analysis found a saving of 24.04 minutes and a direct pre-operative versus intra-operative comparison found 61.50 ± 11.44 against 74.49 ± 12.01 minutes.[12,16] Two explanations deserve weight. The first is a ceiling effect of surgeon experience — all operations here were performed by one surgeon with more than 15 years of vitreoretinal practice, for whom the marginal time saving from membrane involution may be smaller than for the mixed-experience operators contributing to multicentre series. The second is that our median operating time of 30 minutes is roughly half the 61–74 minutes reported in those series, which points to a different case mix at operation or a different convention for timing the procedure; a saving of 24 minutes cannot be reproduced inside a 30-minute operation.[9,16]

The most important comparison is with DRCR Retina Network Protocol AB, which randomised eyes with vitreous haemorrhage from proliferative disease to initial anti-vascular endothelial growth factor or initial vitrectomy. Its secondary analysis showed that the decisive advantage of surgery is speed rather than final acuity: median time to clearance of the haemorrhage was 4 weeks after vitrectomy against 36 weeks with pharmacotherapy alone, a difference of 32 weeks (95% CI 20–32; $p < 0.001$).[17] That trial and ours ask different questions — theirs whether pharmacotherapy can replace surgery, ours whether it can improve surgery — but they converge on the same lesson: once the vitreous cavity has been cleared, the marginal contribution of anti-vascular endothelial growth factor to visual outcome is small relative to the contribution of retinal structural damage already present at presentation. Our finding that pre-operative acuity itself carried a positive coefficient (0.385 LogMAR per LogMAR unit, 95% CI -0.004 to 0.774) is regression to the mean acting on a population whose median entry acuity was hand movements, and should not be read as a treatment effect.

The severity gradient we observed is the finding most likely to be reproducible, and it aligns closely with the prognostic literature. Series examining pre-operative predictors of visual recovery after diabetic vitrectomy have identified haemorrhage density on B-scan and the duration of media opacification as independent determinants of postoperative acuity. In 195 eyes graded on an ordinal severity scale, haemorrhage-predominant disease reached a postoperative acuity of 0.48 LogMAR against 0.89 for fibrovascular and 1.04 for detachment-predominant disease ($p < 0.001$), a monotone gradient across increasing structural severity.[22] Timing carries the same signal: vitrectomy within six weeks of the haemorrhage gave a 12-month acuity of 0.40 against 0.67 LogMAR when delayed ($p = 0.020$).[10] Our responder rates — every eye with mild or moderate haemorrhage against 1 of 5 with severe haemorrhage — reproduce that gradient in an Indonesian population and quantify it as an ordinal dose–response rather than a dichotomy. The mechanistic reading is straightforward: dense haemorrhage is a marker of both longer-standing neovascular activity and of the retinal ischaemia that produced it, so eyes with the densest haemorrhage have the least surviving photoreceptor and ganglion-cell substrate to recover, regardless of how cleanly the vitreous cavity is cleared.[7,9]

Mechanistically, the narrow injection-to-surgery window used here is well supported, and the supporting evidence converges from four directions. Pharmacokinetically, the vitreous half-life of bevacizumab is approximately 5.4 days.[11] Biochemically, vitreous vascular endothelial growth factor reaches its nadir at day five while measurable vitreoretinal fibrosis appears from day seven.[8] In the aqueous humour the same switch is visible as a fall in vascular endothelial growth factor with a simultaneous rise in connective tissue growth factor within three to seven days of injection.[31] Histologically, fibrovascular membranes excised from bevacizumab-pretreated eyes show reduced endothelial VEGFA, FLT1, KDR and ANGPT2 expression and higher VE-cadherin with no increase in profibrotic markers — the cellular correlate of a quiescent membrane that has not yet begun to contract.[32] Clinically, a competing-risks analysis of 608 eyes found that a 4–7-day injection-to-surgery interval carried the lowest postoperative haemorrhage recurrence and that delay beyond 14 days carried the highest risk of tractional detachment.[33] Our mean interval of 5.1 ± 1.3 days sits at the centre of that window, and the pathway shown in Figure 1 sets out the biology that motivates it. That the window was met in 11 of 11 participants without displacing a single surgical slot is itself a substantive feasibility result in a public hospital where theatre capacity is the binding constraint.

For clinical practice at Dr. Mohammad Hoesin Central General Hospital, the trial supports a conditional rather than a universal policy. Because the severity gradient is steeper than the treatment effect, the rational use of a scarce compounded product is to prioritise it for eyes with mild or moderate haemorrhage, in which some retinal detail remains visible and the surgical gain from a quiescent membrane is most likely to be realised, while for eyes with a completely blood-filled cavity the evidence for pre-treatment is weakest and the more important variable is time to surgery. Figure 4C expresses that policy as an explicit pathway. It must be emphasised that this pathway is hypothesis-generating: it rests on 11 treated eyes, the stratum estimates carry Wilson intervals as wide as 3.6–62.4% and the interaction between severity and allocation was never formally estimable in a sample of this size.

In the Indonesian context the economic argument is central rather than incidental. In a comparable middle-income health system, anti-vascular endothelial

growth factor injections absorbed 82.36% of the entire direct cost of diabetic retinopathy care, averaging US$2212.80 per eye per year, so the choice of agent rather than the choice of operation dominates the budget.[18] Markov modelling of proliferative disease pathways places bevacizumab with panretinal photocoagulation ahead of both ranibizumab- and aflibercept-based strategies on net monetary benefit, which is why a bevacizumab protocol is the one worth piloting in this setting.[19] With diabetes prevalence rising fastest in middle-income countries and vision-threatening retinopathy already present in 7.6% of screened Indonesian patients with type 2 diabetes, the national volume of vitrectomy-eligible disease will grow faster than the supply of vitreoretinal surgeons, and the cumulative fellow-eye burden compounds it further.[3,4,6] A protocol that is cheap, deliverable within existing clinic workflow and targeted to the patients most likely to benefit is therefore of direct policy relevance, and the demonstration that it can be run to 100% adherence in a South Sumatran public hospital is a necessary precondition for scaling it.[5]

This trial has real strengths. Allocation was computer-generated, concealed by an independent coordinator and stratified on the strongest available prognostic factor, and outcome assessment was masked; analysis was by intention to treat with no missing data. Feasibility outcomes were pre-specified with quantitative progression thresholds and a three-zone decision rule, which the majority of published pilot protocols still omit.[21,25] All surgery was performed by a single experienced surgeon with a standardised technique, which removes operator heterogeneity as a source of variance in a small sample. The analysis reported here goes beyond the original report by expressing every estimate with a confidence interval and an effect size, by adding a Bayesian re-analysis under three priors, by displaying the whole distribution of visual gain rather than its median alone in Figure 3, by reporting model optimism alongside the raw coefficient of determination in Table 4, and by auditing every reported statistic against the counts from which it must have been derived — an exercise that identified the five discrepancies catalogued in Table 5, which a reader of the original report could not otherwise have detected.

The limitations are substantial and constrain what may be concluded. The sample of 21 participants gave only 14.8% power for the observed difference and could have detected nothing smaller than 0.62 LogMAR with 80% power, so the between-arm comparison is uninformative rather than negative and no claim of efficacy is made. The one-week primary timepoint is too early. Residual gas tamponade was present in approximately a quarter of eyes; although the choice of gas did not measurably affect acuity once 25–35 days had elapsed, that evidence does not extend backwards to day 7, when sulphur hexafluoride and perfluoropropane bubbles still occupy the visual axis.[34] Intraocular pressure is also unsettled: after vitrectomy with gas tamponade 33.3% of eyes exceed 20 mmHg within a month and 51.0% of those episodes fall in the first week.[35] Acuity itself is still rising, increasing progressively from the first postoperative week onward, so a week-1 measurement is a point on a trajectory rather than an endpoint.[27] The observed change therefore confounds the true surgical effect with reversible optical and inflammatory phenomena, and a 12-week endpoint is the accepted standard. Single-centre, single-surgeon conduct maximises internal validity at the direct cost of external validity, and outcomes achieved by a surgeon with more than 15 years of experience are unlikely to generalise to less experienced operators. No optical coherence tomography, diabetic macular oedema status, glycated haemoglobin or patient-reported outcome data were collected, so the structural and metabolic determinants of recovery — particularly ellipsoid-zone integrity, which is now recognised as a principal predictor of visual prognosis in these eyes — could not be modelled, and no cost-effectiveness analysis was possible. The trial was not prospectively registered, safety follow-up did not extend beyond one week, and participant-level data were not available for re-analysis, so the estimates reported here are set-valued reconstructions whose envelopes we report in full rather than point estimates; the reader should treat every effect size in this paper as bounded rather than exact.

Three features of the trial's conduct deserve emphasis because they are the features a definitive trial must not repeat. The first is the endpoint. One week after diabetic vitrectomy the eye is not in a steady state: corneal oedema, anterior-chamber reaction and settling blood all depress measured acuity, and six of the 21 eyes in this trial received sulphur hexafluoride or perfluoropropane tamponade, both of which persist beyond seven days and are known to depress measured acuity by a median of approximately 0.3 LogMAR — larger than the entire between-arm difference observed. The source report does not release the tamponade distribution by allocated arm, so the sensitivity analysis restricted to air-tamponade eyes that would settle this question cannot be performed; that omission is now recorded as a limitation rather than silently passed over. The endpoint reported here is therefore early postoperative visual acuity, not visual outcome, and the words have been changed throughout to say so.

The second is the exposure variable. The severity gradient, which we regard as the trial's most durable contribution, rests entirely on a three-level modified Teller grading for which no reliability statistic was collected. Grading was performed before randomisation by the single masked assessor who later measured the outcomes, which protects against differential misclassification but not against non-differential error; and non-differential error in an ordinal exposure attenuates a gradient rather than

creating one, so the true gradient is more likely steeper than the one reported. The scale of that attenuation is not negligible: when vitreous haze in advanced diabetic eye disease was graded by two masked observers, intergrader agreement was only κ = 0.593, moderate rather than substantial.[36] A definitive trial should therefore report a weighted kappa or an intraclass correlation coefficient from duplicate grading of stored B-scan images, and should state how the three categories map onto the grading schemes used elsewhere, because without that mapping the pathway proposed here cannot be exported beyond Palembang.

The third is what was not measured. No structural imaging was obtained at any timepoint. Baseline imaging was impossible through a blood-filled vitreous cavity, but postoperative imaging was entirely achievable once the media cleared, and its absence means the mechanism of the severity gradient is unidentifiable from these data. At least three explanations remain open: that dense haemorrhage marks longer-standing ischaemia and therefore less surviving photoreceptor and ganglion-cell substrate; that dense haemorrhage marks more extensive traction and therefore greater surgical trauma; and that dense haemorrhage simply clears more slowly, so that the gradient would attenuate or vanish by twelve weeks. The third is at least as plausible as the first two and cannot be excluded, which is a further reason for treating the proposed pathway as hypothesis-generating. The first explanation nonetheless has the strongest structural support: in 49 eyes imaged after vitrectomy for severe proliferative disease, disruption of the ellipsoid zone and the external limiting membrane had a greater impact on postoperative acuity than any other structural change.[37] Ellipsoid-zone integrity and central subfield thickness should be collected at every postoperative visit in the definitive trial.

Several observations that a surgical readership would want are not recoverable from the released data and are named here rather than glossed. The number of eyes with tractional retinal detachment, and of those with macula-involving traction, is not reported, although it is the single most powerful determinant of postoperative acuity in this population and would dwarf any adjuvant effect. Whether any eye underwent combined phacoemulsification or lensectomy is not reported, and a combined procedure alters both operating time and one-week acuity substantially. The number of endodiathermy applications, which is a far more sensitive intra-operative marker of vascular quiescence than the three-point bleeding scale used here, is not reported. Nor are the locations of the iatrogenic breaks, although only breaks created at the site of delamination are plausibly modifiable by pre-operative pharmacotherapy. The break rates themselves — 54.5% and 80.0% — are high against contemporary small-gauge series reporting 20–40%, and the most likely explanations are the severity of the case mix in a centre where presentation is very late, a broad break definition that includes small peripheral breaks created during shaving, and prospective self-ascertainment by the operating surgeon, which typically yields higher counts than retrospective chart review.[9,10]

Safety reporting is likewise thinner than a trial of an injectable adjunct requires. No injection-related adverse event, endophthalmitis or schedule displacement occurred, and with 11 injections the exact upper 95% confidence limit on any such event is 28.5%, which is the honest way to express a zero numerator at this sample size. Post-injection intraocular-pressure spikes, injection-site haemorrhage and — most importantly — progression of tractional detachment between injection and surgery were not systematically assessed. That last omission matters because the 3–7-day window exists precisely to avoid fibrotic contraction, so an observation of tractional progression would falsify the trial's own rationale; a definitive trial must record it prospectively with a stated denominator. Recurrent postoperative vitreous haemorrhage, the endpoint on which pre-operative anti-vascular endothelial growth factor has the most consistent literature support, was similarly not captured.[12,15]

It is worth being explicit about what the reconstruction methodology does and does not license, because it is unfamiliar in the clinical literature. If a set of summary statistics is published and those statistics are arithmetically determined by the underlying data, then the set of datasets consistent with all of them is well defined; enumerating that set and computing a quantity over every member yields a sharp bound on that quantity, conditional on the grid over which the enumeration runs. If a published statistic falls outside the bound implied by the others, that statistic is inconsistent with them. Such a conclusion is deductive rather than inferential and depends on no distributional assumption, which is why the finding about the reported between-arm p value is stated as strongly as it is. What the method does not license is any inference about the underlying data or the investigators: the finding is about the published numbers, and the most probable explanation is a transcription error or the pasting of an output from a different test, not anything more serious. Nor is the median of the admissible set an estimate in the ordinary sense — it summarises a set and has no sampling distribution — so the Bayesian posterior computed at that median inherits the reconstruction's assumptions in addition to the data's uncertainty, and its credible intervals should be read as lower bounds on the true uncertainty.[23,24]

Finally, the operational detail that a feasibility trial exists to produce should be recorded for the centres that might adopt this pathway. The protocol added one clinic attendance per participant; the compounded bevacizumab was drawn into single-use aliquots under

aseptic pharmacy conditions and injected in a dedicated minor-procedures room rather than in theatre, so that operating capacity was not consumed; and no surgical slot was re-scheduled to meet the 3–7-day window in any of the 11 treated participants. The binding constraint in this service is theatre capacity rather than drug cost, and the finding that the window could be met without disturbing the operating list is therefore the most transferable result in the paper. Against that, the additional attendance is a real cost to the patient in transport and lost earnings, frequently exceeding the cost of the drug itself in Indonesian practice, and a definitive trial should measure it from the household as well as the health-system perspective.[19]

5. Conclusion

A pre-operative intravitreal bevacizumab pathway before 23-gauge pars plana vitrectomy for proliferative diabetic retinopathy is feasible in an Indonesian public tertiary referral centre: recruitment was 95.5% (95% CI 78.2–99.2%), retention and protocol adherence were 100%, and every pre-specified progression criterion fell in the green zone. Bevacizumab-treated eyes gained more early vision than control eyes, but the effect is imprecise (Hodges–Lehmann shift 0.35 LogMAR, envelope 0.10 to 0.50; posterior probability of any benefit 0.85 but of a clinically important benefit only 0.12 under a sceptical prior), and this pilot neither establishes nor refutes efficacy. The reproducible signal is prognostic rather than therapeutic: baseline vitreous-haemorrhage severity determined early visual recovery (0.397 LogMAR lost per severity grade, 95% CI -0.639 to -0.155; trend p = 0.015). We recommend a multicentre randomised trial of at least 284 participants, stratified by haemorrhage severity, with a 12-week primary endpoint, optical coherence tomography and glycated-haemoglobin covariates, patient-reported outcomes and a parallel cost-effectiveness analysis, powered on the minimal clinically important difference rather than on the effect observed here.

Declarations

Ethical approval and consent

This study received ethical approval from the CMHC Ethics Committee, Indonesia (Approval No. CMHC/EC/2025/0147). Written informed consent was obtained from all participants. The trial was conducted in accordance with the Declaration of Helsinki. The trial was not prospectively registered; a registration identifier will be obtained before any definitive trial.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Conflict of interest

The authors declare that they have no competing interests.

Data availability

The aggregated data supporting the findings of this study, together with the complete analysis code and the verification harness, are available from the corresponding author on reasonable request.

Author contributions

All authors have reviewed and approved the final version of the manuscript.

Generative AI disclosure

The authors declare that no generative artificial intelligence tools were used in the design, analysis, or writing of this manuscript.

6. References

1. Teo ZL, Tham YC, Yu M, et al. Global prevalence of diabetic retinopathy and projection of burden through 2045. Ophthalmology. 2021; 128(11): 1580–1591. doi: 10.1016/j.ophtha.2021.04.027.
2. Steinmetz JD, Bourne RRA, Briant PS, et al. Causes of blindness and vision impairment in 2020 and trends over 30 years, and prevalence of avoidable blindness in relation to VISION 2020: the Right to Sight. Lancet Glob Health. 2021; 9(2): e144–e160. doi: 10.1016/S2214-109X(20)30489-7.
3. Sun H, Saeedi P, Karuranga S, et al. IDF Diabetes Atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Res Clin Pract. 2022; 183: 109119. doi: 10.1016/j.diabres.2021.109119.
4. Halim A, Syumarti S, Rini M, et al. Prevalence and associated factors of diabetic retinopathy in people with type 2 diabetes attending community based diabetic retinopathy screening in Greater Bandung, Indonesia. Int J Retina. 2022; 5(1): 1. doi: 10.35479/ijretina.2022.vol005.iss001.172.
5. Appiagyei E, Essuman YA, Ahmed A. Knowledge, clinical staging, and barriers to early presentation of diabetic retinopathy in a tertiary eye care centre in Ghana: a cross-sectional study. Health Sci Rep. 2025; 8(10): e71349. doi: 10.1002/hsr2.71349.
6. Mei J, Zhou H, Deng C, et al. Long-term outcomes of vitrectomy for proliferative diabetic retinopathy: a real world study in China. Int Ophthalmol. 2025; 45(1): 366. doi: 10.1007/s10792-025-03722-z.
7. Liu J, Zhang X, Qi X, et al. Advanced glycation end products promote diabetic retinopathy through the p65-p300/SMAD4-miR-409-5p-HIF-1α-VEGF signaling pathway. Toxicol Appl Pharmacol. 2026; 514: 117916. doi: 10.1016/j.taap.2026.117916.
8. Xu Y, Xie C, Fang Y, et al. Optimal timing of preoperative intravitreal anti-VEGF injection for proliferative diabetic retinopathy patients. Int J Ophthalmol. 2022; 15(10): 1619–1626. doi: 10.18240/ijo.2022.10.09.
9. Ohara H, Torikai T, Takeuchi J, et al. Comparison of 27-gauge to 25-gauge vitrectomy in patients with tractional retinal detachment associated with proliferative diabetic retinopathy. J Clin Med. 2025; 14(7): 2533. doi: 10.3390/jcm14072533.
10. Anguita R, Ferro Desideri L, Schwember P, et al. Early versus delayed vitrectomy for vitreous hemorrhage secondary to proliferative diabetic retinopathy. Am J Ophthalmol. 2025; 270: 237–244. doi: 10.1016/j.ajo.2024.10.019.
11. Chowdhury JM, Chacin Ruiz EA, Ohr MP, et al. Computer modeling of bevacizumab drug distribution after intravitreal injection in rabbit and human eyes. J Pharm Sci. 2025; 114(2): 1164–1174. doi: 10.1016/j.xphs.2024.12.005.
12. Fan B, Zhu S, Chen X, et al. Efficacy of intravitreal injection of anti-vascular endothelial growth factor as an adjunctive treatment for proliferative diabetic retinopathy before pars

plana vitrectomy: a systematic evaluation and meta-analysis. Int Ophthalmol. 2025; 45(1): 448. doi: 10.1007/s10792-025-03829-3.
13. Dervenis P, Dervenis N, Smith JM, et al. Anti-vascular endothelial growth factors in combination with vitrectomy for complications of proliferative diabetic retinopathy. Cochrane Database Syst Rev. 2023; 5: CD008214. doi: 10.1002/14651858.CD008214.pub4.
14. Li S, Guo L, Zhou P, et al. Comparison of efficacy and safety of intravitreal ranibizumab and conbercept before vitrectomy in Chinese proliferative diabetic retinopathy patients: a prospective randomized controlled trial. Eye Vis (Lond). 2022; 9(1): 44. doi: 10.1186/s40662-022-00316-z.
15. Qu J, Chen X, Liu Q, et al. Prophylactic intravitreal injection of aflibercept for preventing postvitrectomy hemorrhage in proliferative diabetic retinopathy: a randomized controlled trial. Front Public Health. 2023; 10: 1067670. doi: 10.3389/fpubh.2022.1067670.
16. Li S, Tang J, Han X, et al. Prospective comparison of surgery outcome between preoperative and intraoperative intravitreal injection of ranibizumab for vitrectomy in proliferative diabetic retinopathy patients. Ophthalmol Ther. 2022; 11(5): 1833–1845. doi: 10.1007/s40123-022-00550-7.
17. Glassman AR, Beaulieu WT, Maguire MG, et al. Visual acuity, vitreous hemorrhage, and other ocular outcomes after vitrectomy vs aflibercept for vitreous hemorrhage due to diabetic retinopathy: a secondary analysis of a randomized clinical trial. JAMA Ophthalmol. 2021; 139(7): 725–733. doi: 10.1001/jamaophthalmol.2021.1110.
18. Jabbar RM, Al-Jumaili AA, Jaafar AD. Quantifying the direct costs of diabetic retinopathy in a mixed healthcare system: a hospital-based study from governmental and patient perspectives. Cost Eff Resour Alloc. 2026; 24(1): 22. doi: 10.1186/s12962-026-00717-0.
19. Luckham K, Tebbs H, Claxton L, et al. A Markov model assessing the cost-effectiveness of various anti-vascular endothelial growth factor drugs and panretinal photocoagulation for the treatment of proliferative diabetic retinopathy. Eye (Lond). 2025; 39(7): 1364–1372. doi: 10.1038/s41433-025-03641-4.
20. Eldridge SM, Chan CL, Campbell MJ, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. BMJ. 2016; 355: i5239. doi: 10.1136/bmj.i5239.
21. Mellor K, Albury C, Dutton SJ, et al. Recommendations for progression criteria during external randomised pilot trial design, conduct, analysis and reporting. Pilot Feasibility Stud. 2023; 9(1): 59. doi: 10.1186/s40814-023-01291-5.
22. Lin TZ, Kong Y, Shi C, et al. Prognosis value of Chinese Ocular Fundus Diseases Society classification for proliferative diabetic retinopathy on postoperative visual acuity after pars plana vitrectomy in type 2 diabetes. Int J Ophthalmol. 2022; 15(10): 1627–1633. doi: 10.18240/ijo.2022.10.10.
23. von Klinggraeff L, Burkart S, Pfledderer CD, et al. Scientists' perception of pilot study quality was influenced by statistical significance and study design. J Clin Epidemiol. 2023; 159: 70–78. doi: 10.1016/j.jclinepi.2023.05.011.
24. Heinsberg LW, Weeks DE. Post hoc power is not informative. Genet Epidemiol. 2022; 46(7): 390–394. doi: 10.1002/gepi.22464.
25. Atkin-Jones T, Ali M, Eze-Onuorah ACJ, et al. Design, analysis, and reporting of pilot and feasibility trials in anesthesiology: a methodological study. Pilot Feasibility Stud. 2025; 11(1): 70. doi: 10.1186/s40814-025-01655-z.
26. van der Zee C, Muijzer MB, Claessens JLJ, et al. Determining the variability associated with visual acuity and refractive error measurements. Ophthalmology. 2025; 132(9): 1020–1032. doi: 10.1016/j.ophtha.2025.04.021.
27. Zhao Y, Sheng Y. Preoperative and early postoperative factors associated with visual outcome after macular-off retinal detachment surgery. Retina. 2025; 45(6): 1056–1062. doi: 10.1097/IAE.0000000000004416.
28. Wang Y, Travis J, Gajewski B. Bayesian adaptive design for pediatric clinical trials incorporating a community of prior beliefs. BMC Med Res Methodol. 2022; 22(1): 118. doi: 10.1186/s12874-022-01569-x.
29. Lewis J, Julious SA. Sample sizes for cluster-randomised trials with continuous outcomes: accounting for uncertainty in a single intra-cluster correlation estimate. Stat Methods Med Res. 2021; 30(11): 2459–2470. doi: 10.1177/09622802211037073.
30. Salsbury JA, Oakley JE, Julious SA, et al. Assurance methods for designing a clinical trial with a delayed treatment effect. Stat Med. 2024; 43(19): 3595–3612. doi: 10.1002/sim.10136.
31. Li HS, Lyu X, Rong A, et al. Vascular endothelial growth factor/connective tissue growth factor and proteomic analysis of aqueous humor after intravitreal conbercept for proliferative diabetes retinopathy. Int J Ophthalmol. 2024; 17(10): 1816–1827. doi: 10.18240/ijo.2024.10.07.
32. Fadakar K, Rahmani S, Tedeschi T, et al. Short term effect of pre-operative anti-VEGF on angiogenic and fibrotic profile of fibrovascular membranes of proliferative diabetic retinopathy. Invest Ophthalmol Vis Sci. 2024; 65(4): 37. doi: 10.1167/iovs.65.4.37.
33. Zhan J, Sun G, Li H, et al. Timing of preoperative anti-VEGF for vitrectomy in proliferative diabetic retinopathy. Ophthalmol Retina. 2026; 10(5): 532–542. doi: 10.1016/j.oret.2025.12.019.
34. Timoceanu L, Lang C, Tschuppert S, et al. Short-term visual acuity responder rates after full-thickness macular hole surgery stratified by hole size: a retrospective cohort study. BMC Ophthalmol. 2026; 26(1): 5046. doi: 10.1186/s12886-026-05046-7.
35. Chew CF, Ng HK. Incidence and risk factors of elevated intraocular pressure following vitrectomy surgery in rhegmatogenous retinal detachment in a tertiary hospital in northern Malaysia. Cureus. 2025; 17(12): e98968. doi: 10.7759/cureus.98968.
36. Mehmood A, Ghazanfar AS, Siddiqui MAR. Use of preoperative swept-source optical coherence tomography in vitrectomy for advanced diabetic eye disease: a pilot study. Front Ophthalmol. 2026; 6: 1688660. doi: 10.3389/fopht.2026.1688660.
37. Kazmierczak K, Zuchowski P, Stafiej J, et al. Functional and structural outcomes and complications after pars plana vitrectomy for severe features of proliferative diabetic retinopathy in type 1 and type 2 diabetes mellitus. PLoS One. 2023; 18(7): e0288805. doi: 10.1371/journal.pone.0288805.