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Treat-and-Extend vs. Fixed-Interval Anti-vascular Endothelial Growth Factor (Anti-VEGF) Regimens for Treatment-Naïve Neovascular Age-Related Macular Degeneration (nAMD): A Targeted Review and Meta-Analysis of Randomized Trials

Nawar K. Alkhalifa [1]

1. Internal Medicine, Royal Medical Services, Bahrain Defense Force Hospital, Riffa, BHR

Corresponding author: Nawar K. Alkhalifa, nawaralkhalifa501@gmail.com

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Abstract

Intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy is the standard treatment for neovascular age-related macular degeneration (nAMD), a leading cause of irreversible central vision loss in older adults. Frequent injections and visits burden patients, caregivers, and clinics, and treat-and-extend (T&E) dosing, which individualizes the interval between injections, may reduce that burden.

The study aimed to compare 12-month visual outcomes of T&E with fixed-interval dosing of the same anti-VEGF agent in treatment-naïve adults with nAMD, against a non-inferiority margin of five Early Treatment Diabetic Retinopathy Study (ETDRS) letters. Randomized trials were identified by a targeted (non-systematic) search; screening, data extraction and risk-of-bias assessment were done by one reviewer, and the review was not prospectively registered. Mean differences in best-corrected visual acuity (BCVA) change were pooled by random-effects meta-analysis (REML with Hartung-Knapp confidence intervals) and reported separately by comparator (monthly versus bimonthly/8-weekly).

Five randomized trials were pooled (1,536 participants in the compared arms). The pooled difference was 0.1 letters (95% CI −2.4 to 2.6; 95% prediction interval −6.4 to 6.6; I^2 = 56%). Against monthly ranibizumab (three trials), the difference was 0.5 letters (95% CI −5.5 to 6.4; I^2 = 77%), and T&E used 2.4 to 2.9 fewer injections in year one. Against bimonthly or 8-weekly dosing (two trials), the difference was −0.8 letters (95% CI −4.6 to 2.9), and T&E used 1.7 to 1.9 more injections. Certainty of evidence was low.

Pooled 12-month visual outcomes with T&E were compatible with non-inferiority to fixed dosing (lower confidence limit above −5 letters), but this does not establish equivalence: the prediction interval extends beyond the margin, and the monthly-comparator interval alone could not exclude a five-letter disadvantage. Injection savings were seen only against monthly dosing. Because of the targeted search, single-reviewer process, and absence of prospective registration, these findings are provisional pending a systematic multi-database review.

Categories: Ophthalmology, Internal Medicine
Keywords: aflibercept, anti-vegf, meta-analysis, neovascular age-related macular degeneration, systematic review, treat-and-extend, visual acuity

Introduction And Background

Neovascular age-related macular degeneration (nAMD) is characterized by the growth of abnormal, leaky vessels beneath the macula. Leakage, bleeding, and scarring damage the macula, which supports central vision, and cause irreversible loss of the vision needed for reading and recognizing faces. Age-related macular degeneration is among the leading causes of vision loss in older adults worldwide, and its burden is projected to grow as populations age [1]. Vascular endothelial growth factor (VEGF) drives the growth and permeability of these vessels; intravitreal anti-VEGF agents (medicines injected into the eye, for example, ranibizumab, aflibercept, bevacizumab, brolucizumab, faricimab and conbercept) bind VEGF and reduce leakage, and they have transformed outcomes for this disease. Benefit, however, depends on repeated injections, and the resulting visits, monitoring and costs place a substantial burden on patients, caregivers and retinal services [2]. Visual acuity is usually reported as best-corrected visual acuity (BCVA) in Early Treatment Diabetic Retinopathy Study (ETDRS) letters; 15 letters equal 3 lines on the chart, so a 5-letter difference is about 1 line.

A fixed-interval regimen gives injections at regular intervals (for example, every 4 weeks or every 8 weeks after 3 monthly loading doses) irrespective of disease activity. In a treat-and-extend (T&E) regimen, every visit includes an injection, and the interval to the next visit is lengthened while the macula remains dry and shortened when disease activity returns. T&E is not a single protocol: the loading phase (two or three

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monthly injections), the extension step (two or four weeks), the activity criteria and the maximum interval (12 weeks in most ranibizumab trials and in TAEWA; 16 weeks in some other aflibercept trials) all differ between trials, and these differences probably explain part of the heterogeneity reported later. Reducing injection and visit frequency matters clinically because it lowers the burden on patients and caregivers, frees clinic capacity and reduces cumulative exposure to injection-related risks, provided vision is not compromised. Non-inferiority means that a regimen is not worse than its comparator by more than a prespecified margin; it is not the same as showing that two regimens are equivalent.

Three meta-analyses have addressed this question. Fallico et al. [3], pooling 4 randomized trials, reported no difference in BCVA at 12 and 24 months. Rosenberg et al. [4], who combined randomized and observational evidence, found similar gains at 1 year (MD −0.08 letters, p = 0.95) and 2 years (MD 0.58 letters, p = 0.62). Based on six randomized trials, Nichani et al. [5] found no significant BCVA difference between T&E and monthly, bimonthly, or PRN (as-needed) strategies. A 2026 network meta-analysis of aflibercept regimens [6] (we have seen only its published summary) also reported broadly similar visual outcomes across regimens. The gap this review addresses is that earlier pooled estimates combined different comparator schedules and were interpreted mainly by statistical significance, and the 2025 aflibercept trial TAEWA was not available to them. This review adds to these in four ways: (i) it includes the 2025 TAEWA trial [7], which compared T&E with fixed 8-weekly aflibercept in treatment-naïve (previously untreated) eyes and did not show non-inferiority; (ii) it is restricted to randomized comparisons with a fixed-interval regimen of the same agent in treatment-naïve eyes, excluding PRN comparators and previously treated populations such as AZURE [8]; (iii) it reports results separately by comparator (monthly versus bimonthly or 8-weekly), because earlier pooled estimates combined them; and (iv) it interprets results against a 5-letter non-inferiority margin, using Hartung-Knapp intervals and a prediction interval, rather than statistical significance alone. Because the search was targeted rather than systematic, this review is best read as a focused update and not as a replacement for a full systematic review.

Research question

The question: can a less burdensome T&E strategy achieve visual results that are not worse than fixed-interval dosing by more than 5 letters?

Review

Methods

Protocol and Reporting

This review was not prospectively registered, and no protocol was published, so none of the analyses can be independently verified as prespecified. The eligibility criteria, primary outcome (12-month BCVA change), effect measure, and non-inferiority margin were defined before data extraction. The analysis plan was refined after the data had been seen: the primary model is REML with Hartung-Knapp intervals, five trials were pooled (In-eye was included once its variance could be derived), and comparator-specific estimates are reported first. These analyses are labelled post hoc. Reporting follows PRISMA 2020 where applicable (Appendix A); items that could not be met because no systematic database search was run are identified there.

Eligibility Criteria

Studies were selected according to the inclusion and exclusion criteria presented in Table *1*.

Criterion	Inclusion criteria	Exclusion criteria
Study design	**Randomized controlled trials**	**Non-randomized studies, retrospective studies, reviews and case series**
Population	Adults with treatment-naïve nAMD, regardless of disease activity	Previously treated populations (for example, Kodjikian et al., 2024 [8]); populations restricted to polypoidal choroidal vasculopathy
Intervention	A T&E anti-VEGF regimen	Trials comparing two T&E strategies, or two drugs within a single T&E protocol
Comparator	A fixed-interval regimen (monthly, or fixed interval per study protocol, such as every 8 weeks after loading) of the same anti-VEGF agent	PRN-only comparators
Outcome	BCVA change data reported or calculable	No relevant visual outcome
Publication date and language	No date or language restrictions	Not applicable

TABLE 1: Inclusion and exclusion criteria

BCVA = best-corrected visual acuity; nAMD = neovascular age-related macular degeneration; PRN = pro re nata (as needed); T&E = treat-and-extend; VEGF = vascular endothelial growth factor.

Information Sources and Search

Planned searches. The intended strategy was a systematic search of MEDLINE (PubMed), Embase, CENTRAL, ClinicalTrials.gov and the WHO ICTRP. These searches were not run. The planned strategies are reproduced in Table *2* and Appendix B for transparency and are marked as not conducted. Searches actually conducted. On 8 October 2026, trials were identified from (i) the reference lists and included studies of three earlier meta-analyses of T&E versus monthly or fixed dosing [3-5], (ii) ClinicalTrials.gov registry records, and (iii) targeted web searches of PubMed-indexed literature for trials published after those meta-analyses. Search terms were deliberately not restricted to comparator terms because abstracts often omit the comparator. On 7 November 2026, the original publications of the included and excluded trials were re-checked and further targeted searches were run for randomized trials of T&E versus fixed aflibercept and for published reports of the trials listed in Appendix C. These checks identified one additional potentially eligible trial (Haga et al. [9]) and one 2026 network meta-analysis [6]; they were not exhaustive and do not substitute for a systematic search. The targeted searches are described in Table *2* at the level of concepts and not as reproducible search strings, and cannot be replicated exactly.

Source	Status	Date searched	Search terms and strategy
MEDLINE (PubMed)	Planned	Not conducted in this version	('macular degeneration' [MeSH Terms] OR 'wet AMD' [tiab] OR 'neovascular AMD' [tiab] OR nAMD[tiab] OR 'exudative age-related macular degeneration' [tiab] OR 'choroidal neovascularisation' [tiab] OR 'angiogenesis inhibitors' [MeSH Terms] OR 'anti-VEGF' [tiab] OR 'ranibizumab' [tiab] OR aflibercept[tiab] OR bevacizumab[tiab] OR brolucizumab[tiab] OR faricimab[tiab] OR conbercept[tiab] OR 'treat and extend' [tiab] OR 'treat-and-extend' [tiab] OR 'inject and extend' [tiab] OR TREX[tiab] OR 'individualized dosing' [tiab] OR 'randomized controlled trial' [pt] OR randomized [tiab] OR 'randomized' [tiab] OR 'trial' [tiab] OR trial[tiab])
Embase (Ovid)	Planned	Not conducted in this version	Same concepts as the MEDLINE strategy, using Emtree terms (exp macular degeneration/; exp vasculotropin inhibitor/), plus T&E and randomized-trial terms.
CENTRAL	Planned	Not conducted in this version	Same keywords as the MEDLINE strategy.
ClinicalTrials.gov and WHO ICTRP	Planned	Not conducted in this version	Intervention terms: “treat and extend” or “treat-and-extend”; condition term: “neovascular age-related macular degeneration”.
Targeted web and literature searches	Conducted	8 October 2026; supplementary checks 7 November 2026	Meta-analyses of T&E versus alternative anti-VEGF regimens; primary results from TREND, CANTREAT and TREX-AMD; T&E versus fixed aflibercept in treatment-naïve nAMD; T&E versus monthly or fixed dosing with conbercept, bevacizumab or faricimab; In-eye and bimonthly ranibizumab; original publications of excluded trials (supplementary checks).
ClinicalTrials.gov	Conducted	8 October 2026	Registry results of the included trials.

TABLE 2: Search strategy (planned and conducted)

AMD = age-related macular degeneration; anti-VEGF = anti-vascular endothelial growth factor; CENTRAL = Cochrane Central Register of Controlled Trials; CANTREAT = Canadian Treat-and-Extend Analysis Trial; exp = explode (include narrower terms); Emtree = Embase subject headings; ICTRP = International Clinical Trials Registry Platform; MEDLINE = Medical Literature Analysis and Retrieval System Online; MeSH = Medical Subject Headings; nAMD = neovascular age-related macular degeneration; pt = publication type; T&E = treat-and-extend; tiab = title and abstract; WHO = World Health Organization. Other trial names are used as published.

Study Selection

One reviewer screened 15 candidate trials (14 from the initial targeted search and 1 added in the supplementary checks) against the eligibility criteria in Table *1*; no second reviewer screened independently, and no third reviewer arbitrated. Multiple reports of one trial (for example, the 1- and 2-year CANTREAT reports [10,11]) were linked. Decisions and reasons are in Appendix C, and the flow of trials is in Figure *1* and Appendix D. The flow diagram reports trial counts only; record-level counts cannot be given because no systematic database search was run.

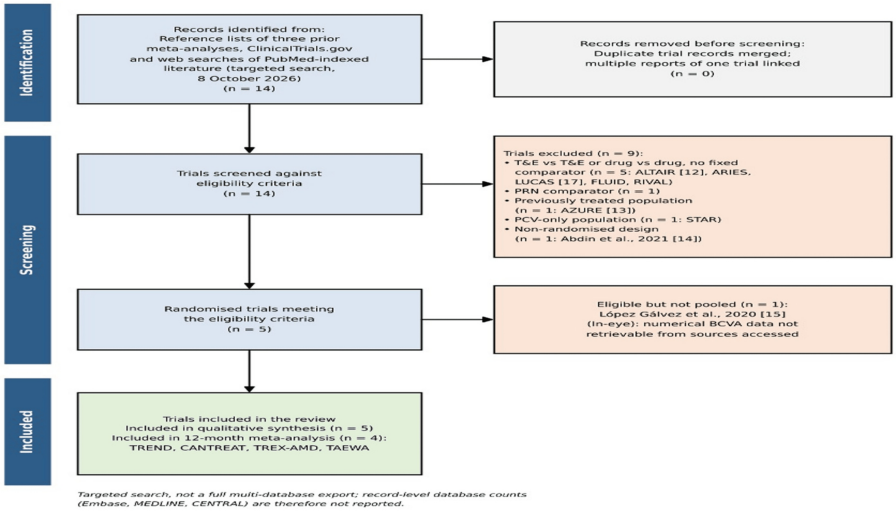


FIGURE 1: PRISMA 2020 flow diagram of trial selection

Data Extraction

Variables extracted were: study year, setting, sample size, anti-VEGF agent, loading schedule, T&E extension rules, fixed schedule, baseline BCVA, change in BCVA, injection numbers, retinal thickness, proportions gaining or losing 15 or more letters, adverse events and follow-up. One reviewer extracted data from published reports and registry results. The key inputs for CANTREAT, TREX-AMD, TAEWA and In-eye were checked against the original publications or their abstracts; TREND inputs were not checked against the full text. No second reviewer verified the extraction. Extracted values and derivations are in Appendix E.

Unit of Analysis and Multi-arm Trials

Participant-level outcomes were sought. Where both eyes were enrolled, the statistical method used in the trial was kept. Each trial contributed one comparison of T&E with a fixed-interval regimen. In the three-arm In-eye trial, the T&E and bimonthly arms were compared, and the PRN arm was not used, so no arm was counted twice [12].

Effect Sizes and Missing Variance

The effect measure was the mean difference (MD) in 12-month BCVA change (ETDRS letters), T&E minus fixed. Standard errors (SE) were taken, in order of preference, from (i) a reported 95% confidence interval, (ii) group SDs and sizes, (iii) arm-level confidence intervals, or (iv) a reported p-value with a normal approximation [12]. TREND: SE 0.995 from the published 95% CI (−3.83 to 0.07; MD −1.88, the CI midpoint), which agrees with the registry per-arm SEs of 0.70. CANTREAT: SE 1.054 from the published 95% CI (0.32 to 4.45; MD 2.38) [10], which agrees with the SE of 1.04 calculated from the reported SDs (11.9 and 11.9) and analyzed group sizes (268 and 258). The CANTREAT SE is taken from the published CI and not from the one-sided p = 0.012 reported at a conference presentation, because that p-value comes from a one-sided t-test of superiority against zero difference, not a test of non-inferiority against −5 letters. TAEWA: SE 3.36 from the reported SDs (12.3 and 8.4) and full-analysis-set sizes (28 and 12) [7]; these sizes come from the trial's baseline table (40 of 44 randomized participants were analyzed) and were not assumed. In-eye: arm-level BCVA gains with 95% CIs (T&E 6.4, 2.9 to 9.8; bimonthly 7.2, 4.2 to 10.2) [13] gave arm SEs of 1.76 and 1.53 and a difference of −0.8 with SE 2.33, assuming independent arms. TREX-AMD: SE 2.48 was derived from the two-sided p = 0.60 at 12 months [14]; it is the only remaining derived SE and is probably underestimated (an SD of 12 letters with 40 and 20 participants would give about 3.3), so a sensitivity analysis with SE 3.3 is reported.

Risk of Bias and Certainty

Risk of bias was assessed with the RoB 2 domains [15] by one reviewer. Full texts were read only for TAEWA. For the other trials, the judgements rest on abstracts, registry entries, and secondary reports; they are provisional screening judgements, not complete RoB 2 assessments. Certainty of evidence was judged informally by one reviewer using GRADE domains; it is GRADE-informed and not a formal GRADE assessment.

Outcomes

The main outcome was the MD in BCVA change from baseline at 12 months. Secondary outcomes were BCVA change at 24 months, the proportions gaining or losing 15 or more letters, number of injections, central retinal or central subfield thickness, and adverse events. Secondary outcomes were summarized narratively because pooling was not possible.

Statistical Analysis

Mean differences were pooled with a random-effects model because trials differed in agent, loading regimen, extension algorithm, and comparator interval. Between-trial variance (τ^2) was estimated by restricted maximum likelihood (REML) [16], and 95% confidence intervals used the Hartung-Knapp adjustment with a t distribution on k − 1 degrees of freedom [17,18], because few trials were pooled. DerSimonian-Laird estimates are shown as a sensitivity analysis. Heterogeneity was summarized by Cochran's Q, I^2 [19], and τ^2, and the 95% prediction interval used a t distribution on k − 2 degrees of freedom [20]. Because monthly and bimonthly/8-weekly comparators differ clinically, comparator-specific estimates are presented first (monthly comparator: REML with Hartung-Knapp; bimonthly/8-weekly comparator, two trials: common-effect model), followed by the overall estimate. Sensitivity analyses were leave-one-out analyses, exclusion of In-eye (leaving four trials), and an alternative TREX-AMD SE. Apart from the original DerSimonian-Laird analysis, all analyses are post hoc and are labelled as such. Meta-regression and assessment of publication bias were not performed because five trials are too few. Analyses used Python 3 (NumPy, SciPy); the script is supplementary material and the analytic dataset is in Appendix E.

The non-inferiority margin was −5 ETDRS letters (about one chart line), the margin used in TREND, CANTREAT, TAEWA and In-eye. T&E was judged compatible with non-inferiority if the lower limit of the Hartung-Knapp confidence interval exceeded −5 letters, and the prediction interval was used to judge whether this would hold in a new setting. The margin was taken from the included trials, not derived independently for this review, and the review was not registered, so this judgement is descriptive. Non-significance was not taken as evidence of equivalence, and no formal equivalence test was done.

Results

Study Selection

Fifteen candidate trials were assessed (Figure *1*, Appendices C, D). Nine were excluded: five had no fixed-interval comparator (three compared two T&E strategies, ALTAIR [21], ARIES [22] and FLUID [23], and two compared two drugs both under T&E, LUCAS [24] and RIVAL [25]); one used a PRN comparator (conbercept; Jia et al. [26]); one enrolled previously treated patients (AZURE [8]); one enrolled only patients with polypoidal choroidal vasculopathy (STAR [27]); and one was retrospective and non-randomized (Abdin et al. [28]). Five randomized trials were eligible, and all 5 contributed 12-month BCVA data: TREND [29], CANTREAT [10], TREX-AMD [14], TAEWA [7] and In-eye [13]. In-eye's variance was initially thought to be unavailable, but its original abstract reports arm-level 95% CIs, which allowed the SE of the difference to be derived. One further randomized trial, Haga et al. [9] (T&E versus every-other-month aflibercept, 41 Japanese patients), was identified in the supplementary checks; its treatment-naïve status could not be confirmed from the abstract, so it awaits classification and was not pooled.

Included Studies

Five trials were included (Table *3*). Three compared ranibizumab T&E with monthly ranibizumab (TREND, CANTREAT, TREX-AMD; 1,290 randomized participants), 1 compared aflibercept T&E with fixed 8-weekly aflibercept (TAEWA; 44 participants), and 1 compared ranibizumab T&E with bimonthly ranibizumab (In-eye; 202 participants in these 2 arms, with a separate PRN arm of 104 that was not used). T&E protocols differed: loading was 2 (TREND) or 3 monthly injections, extension steps were 2 or 4 weeks, the maximum interval was 12 weeks in CANTREAT, TREX-AMD, and TAEWA, and activity criteria differed.

Study	Setting and design	T&E regimen	Fixed comparator	Randomised (T&E / fixed)	12-month BCVA change, letters (T&E vs fixed)
Silva et al., 2018 [29] (TREND)	Treatment-naïve nAMD; 90 centres, 18 countries; assessor-masked; 12 months	Ranibizumab 0.5 mg; loading at baseline and month 1 (two doses), then T&E	Ranibizumab 0.5 mg monthly	650 (323 / 327)	+6.2 vs +8.1 (least-squares means); MD −1.9, 95% CI −3.83 to 0.07
Kertes et al., 2019 [10]; Kertes et al., 2020 [11] (CANTREAT)	Treatment-naïve nAMD; 27 centres, Canada; open-label; 24 months (extended to 36)	Ranibizumab 0.5 mg; 3 monthly loading doses, then stepwise extension to a maximum of 12 weeks (shortened by 4 weeks if activity recurred at 10–12-week intervals)	Ranibizumab 0.5 mg monthly	580 (287 / 293); analyzed at 12 months 526 (268 / 258)	+8.4 vs +6.0; MD 2.38, 95% CI 0.32 to 4.45
Wykoff et al., 2015 [14] (TREX-AMD); 2017 [30]; 2018 [31]	Treatment-naïve nAMD; multicentre phase IIIb; 24 months (36-month final report)	Ranibizumab 0.5 mg; at least 3 monthly doses until dry macula, then incremental extension to a maximum of 12 weeks	Ranibizumab 0.5 mg monthly	60 (40 / 20)	+10.5 vs +9.2; MD 1.3 (p = 0.60)
Wu et al., 2025 [7] (TAEWA)	Treatment-naïve nAMD; single centre, Canada; open-label; 12 months	Aflibercept 2 mg; 3 monthly doses, then T&E with 2-week extension steps and 2- or 4-week reductions (4 to 12 weeks)	Aflibercept 2 mg every 8 weeks after loading	44 (32 / 12); full analysis set 40 (28 / 12)	+4.1 (SD 12.3) vs +5.0 (SD 8.4); MD −0.9
López Gálvez et al., 2020 [13] (In-eye)	Treatment-naïve nAMD; multicentre; 12 months; three-arm; non-inferiority design	Ranibizumab 0.5 mg T&E (details not extracted)	Ranibizumab bimonthly (PRN arm also)	99 / 103 (PRN 104)	+6.4 (2.9 to 9.8) vs +7.2 (4.2 to 10.2); MD −0.8, SE 2.33 derived from arm-level CIs (PRN +8.0)

TABLE 3: Characteristics of included trials

BCVA = best-corrected visual acuity; CI = confidence interval; LS = least-squares; MD = mean difference, T&E minus fixed; nAMD = neovascular age-related macular degeneration; PRN = pro re nata (as needed); SD = standard deviation; SE = standard error; T&E = treat-and-extend. CANTREAT = Canadian Treat-and-Extend Analysis Trial. Other trial names are used as published. Sources: see Appendix E.

BCVA at 12 Months

The five trials gave a pooled MD of 0.12 letters (REML with Hartung-Knapp 95% CI −2.39 to 2.62; p = 0.90; Table *4*, Figure *2*), with moderate to substantial heterogeneity (Q = 9.14, df = 4, p = 0.058; I^2 = 56%; τ^2 = 2.94). The lower confidence limit was above the −5-letter margin, but the 95% prediction interval (−6.4 to 6.6) was not. By comparator, the 3 monthly-comparator trials gave an MD of 0.45 letters (95% CI −5.46 to 6.37; I^2 = 77%; the Hartung-Knapp interval rests on 2 degrees of freedom and is wide, and the REML Wald interval was −2.51 to 3.42), whereas the 2 bimonthly or 8-weekly trials gave −0.83 letters (95% CI −4.59 to 2.92; I^2 = 0%; common-effect model). TAEWA alone gave −0.90 letters (95% CI −7.48 to 5.68) and did not meet its own non-inferiority criterion (p = 0.096) [7]; In-eye alone gave −0.80 (95% CI −5.37 to 3.77).

Analysis	Trials	MD	95% CI	I²
Overall: REML + Hartung–Knapp (primary; post hoc)	5	0.12	−2.39 to 2.62	56%
Overall: REML, Wald CI (post hoc)	5	0.12	−2.07 to 2.31	56%
Overall: DerSimonian–Laird, Wald CI (original method)	5	0.12	−2.16 to 2.39	56%
Monthly comparator (TREND, CANTREAT, TREX-AMD): REML + Hartung–Knapp (post hoc)	3	0.45	−5.46 to 6.37	77%
Bimonthly/8-weekly comparator (TAEWA, In-eye): common-effect (post hoc)	2	−0.83	−4.59 to 2.92	0%
TAEWA alone	1	−0.90	−7.48 to 5.68	n/a
In-eye alone	1	−0.80	−5.37 to 3.77	n/a
Excluding In-eye (four-trial set; REML + HK; post hoc)	4	0.28	−3.19 to 3.76	67%
Excluding TREND (post hoc)	4	1.51	−0.91 to 3.93	0%
Excluding CANTREAT (post hoc)	4	−1.32	−3.20 to 0.55	0%
Excluding TREX-AMD (post hoc)	4	−0.09	−3.50 to 3.32	66%
Excluding TAEWA (post hoc)	4	0.22	−3.18 to 3.62	67%
TREX-AMD SE set to 3.3 (post hoc)	5	0.06	−2.47 to 2.59	56%

TABLE 4: Primary, comparator-specific and sensitivity analyses for the 12-month BCVA mean difference (letters; T&E minus fixed)

BCVA = best-corrected visual acuity; CI = confidence interval; HK = Hartung–Knapp; I² = percentage of variability across trials due to heterogeneity; MD = mean difference in BCVA change (letters), T&E minus fixed; n/a = not applicable; REML = restricted maximum likelihood; SE = standard error; T&E = treat-and-extend. The 95% prediction interval for the primary analysis is −6.4 to 6.6 letters. The Hartung–Knapp interval for the monthly comparator rests on 2 degrees of freedom. The REML Wald interval for that comparator is −2.51 to 3.42. CANTREAT = Canadian Treat-and-Extend Analysis Trial. Other trial names are used as published.

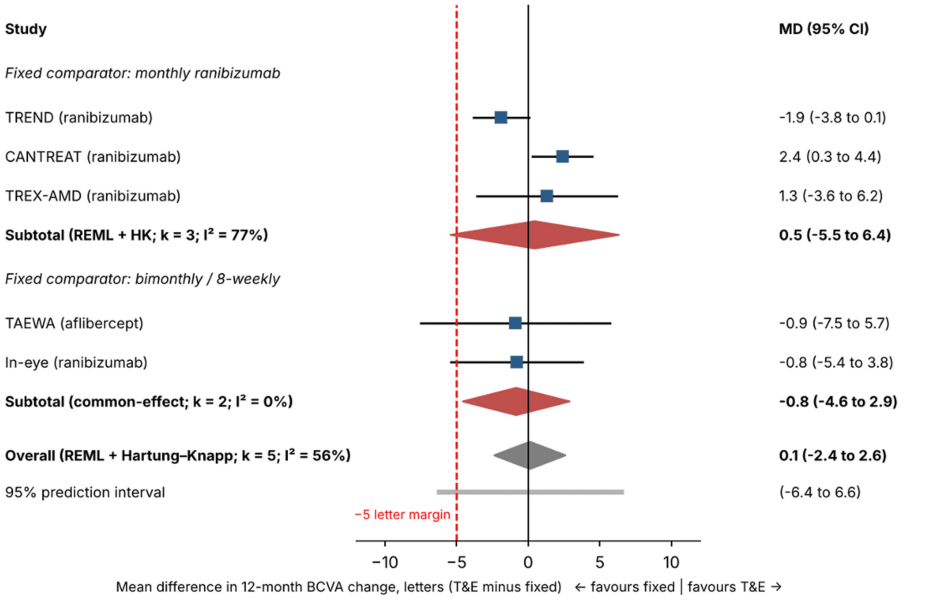


FIGURE 2: Forest plot of the 12-month mean difference in BCVA change (T&E minus fixed), by comparator

Overall estimate: REML with Hartung–Knapp interval; the gray bar is the 95% prediction interval. The dashed line marks the −5-letter margin.

BCVA = best-corrected visual acuity; T&E = treat-and-extend; REML = restricted maximum likelihood

The 2 largest trials pointed in opposite directions: TREND −1.9 letters (95% CI −3.83 to 0.07) and CANTREAT +2.4 letters (95% CI 0.32 to 4.45). Leaving out either removed the heterogeneity (I^2 = 0%) or moved the estimate in opposite directions (excluding CANTREAT −1.32, 95% CI −3.20 to 0.55; excluding TREND +1.51, 95% CI −0.91 to 3.93; Table *4*). Excluding In-eye, which leaves 4 trials, gave 0.28 (95% CI −3.19 to 3.76; I^2 = 67%), and setting the TREX-AMD SE to 3.3 gave 0.06 (95% CI −2.47 to 2.59). Confidence limits in the text, Table *3*, Table *4*, and Figure *2* are all calculated from the same inputs (Appendix E). Table *4* sets out the primary, comparator-specific, and sensitivity analyses.

All analyses other than the original DerSimonian-Laird analysis are post hoc.

BCVA at 24 Months

Pooling at 24 months was not feasible: only CANTREAT and TREX-AMD reported it, and TREX-AMD gave no variance. CANTREAT reported gains of 6.8 (SD 14.1) letters with T&E and 6.0 (SD 12.6) with monthly dosing (difference 0.9; 95% CI −1.6 to 3.3; p = 0.21) [11]. TREX-AMD reported 8.7 letters with T&E and 10.5 with monthly dosing (P = 0.64) [30]; a 36-month report followed [31]. The 12-month advantage of T&E seen in CANTREAT was therefore not evident at 24 months, and in TREX-AMD the point estimate favoured monthly dosing.

Injection Burden

Against monthly ranibizumab, T&E reduced first-year injections in all 3 trials: by 2.4 in TREND (8.7 versus 11.1), by 2.4 in CANTREAT (9.4 versus 11.8) and by 2.9 in TREX-AMD (10.1 versus 13.0). Over 2 years, CANTREAT reported 17.6 versus 23.5 injections (difference 5.9; 95% CI 5.4 to 6.5) [11] and TREX-AMD 18.6 versus 25.5 [30]. Against bimonthly or 8-weekly dosing, the result reversed: T&E required 9.6 ± 2.0 versus 7.7 ± 1.3 injections in TAEWA (p < 0.001) [7] and 9.3 versus 7.6 in In-eye (p < 0.001) [13]. The injection advantage therefore depends on the comparator.

Anatomic Outcomes

Anatomic results were similar. TREND mean change in CSFT was −169.2 µm in T&E and −173.3 µm in monthly dosing. In the TAEWA group, central retinal thickness decreased by 103.7 µm in the T&E group and 131.8 µm in the fixed-dosing group (p = 0.4).

Visual-Gain Outcomes

At 24 months in CANTREAT, 25.5% of T&E and 23.1% of monthly patients gained at least 15 letters (difference 2.4%; 95% CI −6.8% to 11.6%), and 6.5% versus 5.8% lost at least 15 letters [11]. In TREX-AMD at 24 months, 30% of T&E and 20% of monthly patients gained at least 15 letters, whereas 13% of T&E and no monthly patients lost at least 15 letters (small numbers) [30]. In TAEWA, 57% of T&E and 58% of fixed-dosing patients gained 5 or more letters at 12 months, and 1 T&E patient lost 15 or more letters [7]. No pooled estimate was available.

Safety

Safety outcomes were reported inconsistently across studies and are summarized narratively. In TAEWA, 3 patients, all in the T&E arm, had treatment-emergent adverse events (2 cancers and 1 fall requiring hospitalization), none judged related to aflibercept, and no ocular adverse events were reported across 360 injections [7]. Complete safety tables were not extracted for TREND, CANTREAT, TREX-AMD or In-eye.

Risk of Bias and Certainty of Evidence

Provisional risk-of-bias judgements are shown in Table *5*. All trials were open-label with respect to regimen, so deviations from the intended interventions could not be excluded. After reading the full text, TAEWA was judged at high overall risk: randomization took place after the three-dose loading phase, and there were significant baseline imbalances in BCVA and retinal thickness (D1: some concerns); missing data were handled by last observation carried forward, and 4 of 44 randomized participants were excluded from the full analysis set (D3: high). BCVA is a relatively objective endpoint and assessors were masked in TREND. For TREND, CANTREAT, TREX-AMD, and In-eye, the judgements rest on abstracts, registries and secondary reports; they are provisional and are not complete RoB 2 assessments.

Trial	D1 Randomisation	D2 Deviations	D3 Missing data	D4 Measurement	D5 Selection	Overall
Silva et al., 2018 [29] (TREND)	Low	Some concerns	Low	Low	Low	Some concerns
Kertes et al., 2019 [10] (CANTREAT)	Low	Some concerns	Some concerns	Some concerns	Low	Some concerns
Wykoff et al., 2015 [14] (TREX-AMD)	Low	Some concerns	Low	Some concerns	Low	Some concerns
Wu et al., 2025 [7] (TAEWA)	Some concerns	Some concerns	High	Some concerns	Some concerns	High
López Gálvez et al., 2020 [13] (In-eye)	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed

TABLE 5: Provisional risk-of-bias judgements (RoB 2 domains)

RoB 2 = Cochrane Risk of Bias 2 tool; D1 = bias arising from the randomisation process; D2 = bias due to deviations from intended interventions; D3 = bias due to missing outcome data; D4 = bias in measurement of the outcome; D5 = bias in selection of the reported result. TAEWA was judged from the full text. The other ratings are provisional screening judgements from abstracts, registry entries and secondary reports and are not complete RoB 2 assessments; In-eye was not assessed. All ratings by a single reviewer. CANTREAT = Canadian Treat-and-Extend Analysis Trial. Other trial names are used as published.

Certainty of Evidence

Certainty was low for 12-month BCVA (risk of bias; inconsistency, with $I^2 = 56\%$ and a prediction interval crossing the margin), low for fewer injections versus monthly dosing (three trials, not pooled), low for more injections versus bimonthly or 8-weekly dosing (2 trials, one small and at high risk of bias) and low for 24-month BCVA (Table *6*). All ratings are informal judgements by one reviewer.

Outcome	Trials (participants)	Effect (T&E vs fixed)	Certainty and reasons
12-month BCVA (letters)	5 RCTs (1,536 in compared arms)	MD 0.12 (95% CI −2.39 to 2.62; prediction interval −6.4 to 6.6)	Low: risk of bias −1 (open-label; TAEWA high); inconsistency −1 (I^2 56%; prediction interval crosses margin)
12-month injections vs monthly	3 RCTs (1,290)	2.4 to 2.9 fewer with T&E (not pooled)	Low: risk of bias −1 (open-label); imprecision −1 (three trials, not pooled)
12-month injections vs bimonthly/8-weekly	2 RCTs (246)	1.7 to 1.9 more with T&E (TAEWA 9.6 vs 7.7; In-eye 9.3 vs 7.6; not pooled)	Low: risk of bias −1 (open-label; TAEWA high); imprecision −1 (two trials, one n = 44)
24-month BCVA	2 RCTs (640)	Kertes et al., 2020 [11] MD 0.9 (−1.6 to 3.3); TREX-AMD [30] P = 0.64 (not pooled)	Low: risk of bias −1; imprecision/no variance −1

TABLE 6: Informal certainty assessment (GRADE-informed; single reviewer)

BCVA = best-corrected visual acuity; CI = confidence interval; GRADE = Grading of Recommendations Assessment, Development and Evaluation; I^2 = percentage of variability across trials due to heterogeneity; MD = mean difference; RCT = randomized controlled trial; T&E = treat-and-extend. Start high; downgraded one level per concern. Single-reviewer judgement. Trial names are used as published.

Discussion

Across five randomized trials in treatment-naïve nAMD, 12-month BCVA change with T&E did not differ significantly from that with fixed-interval dosing of the same agent (pooled MD 0.1 letters; 95% CI −2.4 to 2.6). The lower confidence limit lies within the −5-letter margin, so the pooled estimate is compatible with non-inferiority. The evidence consists of two large ranibizumab trials (TREND, CANTREAT) and three small trials, with low certainty and moderate heterogeneity.

TREND randomized 650 patients and reported that T&E was non-inferior despite a numerical disadvantage of 1.9 letters (6.2 versus 8.1 letters), with 8.7 versus 11.1 injections over 12 months [29]. CANTREAT showed the opposite direction at 12 months, with a higher gain with T&E (8.4 versus 6.0 letters), but this difference was not present at 24 months (0.9 letters) [10,11]. These two largest trials point in opposite directions and account for most of the heterogeneity; differences in loading (two versus three doses), extension algorithm, and maximum interval may contribute, but with two trials this cannot be tested. Neither regimen can be called visually superior.

The comparator matters. Three trials used monthly ranibizumab, and T&E saved 2.4 to 2.9 injections in year one. The two trials with bimonthly or 8-weekly comparators, TAEWA (aflibercept; small, high risk of bias, baseline imbalance) and In-eye (ranibizumab), both found more injections with T&E (by 1.9 and 1.7) and no visual advantage. The monthly-comparator and bimonthly/8-weekly estimates should therefore be read separately, and the monthly-comparator interval alone (−5.5 to 6.4) cannot exclude a 5-letter disadvantage.

T&E is a family of protocols and not a single one. Loading (two or three monthly injections), extension steps (2 or 4 weeks), activity criteria and the maximum interval (12 weeks in CANTREAT, TREX-AMD and TAEWA; 16 weeks in ALTAIR and ARIES) all differed (Table *3*), and the pooled estimate is an average across these protocols.

Non-Inferiority Interpretation

The non-inferiority margin was −5 letters. The pooled lower limit (−2.39 with the Hartung-Knapp interval) lies within the margin, so the pooled estimate is compatible with non-inferiority. This is not equivalence: no equivalence test was performed, and the absence of a significant difference does not show that regimens are equivalent. The 95% prediction interval (−6.4 to 6.6) extends past the margin, so non-inferiority cannot be assumed for every setting or T&E algorithm; the monthly-comparator interval (−5.46 to 6.37, three trials) also extends past it; and the small, high-risk TAEWA trial did not meet its own non-inferiority criterion (p = 0.096). The margin was taken from the included trials and was not derived independently.

Comparison with Previous Reviews

Our findings are consistent with Fallico et al. [3], Rosenberg et al. [4], and Nichani et al. [5], none of which found a significant BCVA difference, and with fewer injections with T&E than with monthly dosing. This

review differs in including TAEWA, reporting by comparator, giving a prediction interval, and using a non-inferiority margin. A 2026 network meta-analysis of aflibercept regimens [6], seen only as a summary, also reported similar visual outcomes across regimens, and its trial list should be cross-checked in a systematic update. Newer agents were not directly eligible: in TENAYA and LUCERNE, faricimab was dosed at intervals of up to 16 weeks (chosen by protocol-defined disease-activity assessments in year one and by a personalized treat-and-extend regimen in year two) versus fixed 8-weekly aflibercept [32]. Because the comparator was a different drug, these trials do not isolate the effect of the regimen, but they show that extended-interval strategies are being developed with newer agents. Haga et al. [9], a randomized comparison of T&E with every-other-month aflibercept, was identified in the supplementary checks and awaits classification.

Clinical Implications

Where reducing visits relative to monthly dosing is the goal, T&E is a reasonable option that did not appear to cost vision on average, provided follow-up includes visual acuity and OCT testing and intervals are shortened promptly when disease becomes active. With aflibercept, the two available trials showed no first-year injection saving over a fixed eight-weekly schedule, so the choice between T&E and fixed eight-weekly dosing should rest on patient factors and local resources. The small-numbers signal of more losses of 15 or more letters with T&E in TREX-AMD (13% versus 0%) [30] should be borne in mind when monitoring patients.

Strengths

Strengths include a focused question limited to randomized trials in treatment-naïve patients, comparator-specific analyses, effect-size derivations that can be reproduced with the supplied script, checking key inputs against original publications, and reporting of heterogeneity, prediction interval, and sensitivity analyses.

Limitations

The principal limitation is the search: a targeted rather than systematic search was performed, so eligible trials may have been missed, and supplementary checks already identified one such trial (Haga et al. [9]) and a recent network meta-analysis whose trial list was not cross-checked [6]. One reviewer performed screening, data extraction, risk-of-bias assessment and certainty grading, with no independent verification, and the review was not prospectively registered. Risk-of-bias judgements are provisional and, except for TAEWA, not based on full texts, and certainty ratings are informal. Only five trials were pooled, heterogeneity was moderate to substantial (I^2 56% overall, 77% for the monthly comparator), the TREX-AMD SE was derived from a p-value, and the In-eye SE was derived from arm-level CIs assuming independent arms. No 24-month pooling, publication-bias assessment, or meta-regression was possible.

Clinical limitations are differences in agent, loading, extension algorithm, and comparator interval; open-label designs; one small high-risk trial with baseline imbalance; follow-up mostly limited to 12 months; and inconsistent reporting of adverse events. These findings should be confirmed by a systematic multi-database review with dual screening, dual extraction and prospective registration.

Conclusions

In treatment-naïve nAMD, 12-month visual outcomes with treat-and-extend dosing were compatible with non-inferiority to fixed-interval dosing of the same agent (pooled difference 0.1 letters; 95% CI −2.4 to 2.6; non-inferiority margin −5 letters). This does not demonstrate equivalence: the prediction interval (−6.4 to 6.6) extends past the margin, the monthly-comparator estimate alone could not exclude a 5-letter disadvantage, and certainty was low. T&E reduced injections by about 2.4 to 2.9 in year one compared with monthly ranibizumab, but not compared with bimonthly or 8-weekly dosing, where it required more (by 1.7 to 1.9). T&E can reasonably be considered to reduce visit burden relative to monthly dosing, with regular optical coherence tomography and visual acuity monitoring and prompt shortening of the interval when disease is active; the choice of agent, comparator schedule and local resources should be a joint decision between patient and clinician. Future trials should use standardized extension algorithms, masked outcome assessment and patient-centred outcomes such as treatment burden and quality of life. Because of the targeted search, single-reviewer process and absence of prospective registration, these findings are provisional until confirmed by a systematic multi-database review.

Appendices

Appendix A: PRISMA 2020 checklist mapping

Item	Topic	Location
1	Title	Title page
2	Abstract	Abstract
3	Rationale	1. Introduction
4	Objectives	1; 1.1 (PICO table)
5	Eligibility criteria	2.2; Table 1
6	Information sources	2.3 (targeted; partial)
7	Search strategy	2.3; Table 2; Appendix B (partial)
8	Selection process	2.4 (single reviewer; partial)
9	Data collection process	2.5
10	Data items	2.5; 2.9
11	Risk of bias assessment	2.8 (single reviewer; provisional)
12	Effect measures	2.7
13	Synthesis methods	2.6; 2.7; 2.10
14	Reporting bias assessment	2.10 (not assessable, k < 10)
15	Certainty assessment	2.8 (informal; partial)
16	Study selection	3.1; Figure 1; Appendices C and D
17	Study characteristics	3.2; Table 3
18	Risk of bias in studies	3.9; Table 5
19	Results of individual studies	3.3; Figure 2; Table 4
20	Results of syntheses	3.3–3.8; Table 4
21	Reporting biases	5 (not assessable, k < 10)
22	Certainty of evidence	3.10; Table 6
23	Discussion	4; 5
24	Registration and protocol	2.1 (not registered; no protocol)
25	Support	Not reported in manuscript; provided at submission
26	Competing interests	Provided at submission
27	Availability of data and code	Appendix E; ma.py (supplementary file)

TABLE 7: PRISMA 2020 checklist mapping

k = number of trials; ma.py = Python analysis script (supplementary file); PICO = Population, Intervention, Comparator, Outcome; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses. Items 6 to 8, 15 and 16 are only partly met because no systematic search, dual screening or formal GRADE assessment was performed.

Appendix B: search strategies

The planned search strategies (not conducted) and the targeted searches actually conducted are presented in Table *2*.

Appendix C: eligibility decisions for all 15 candidate trials

Trial	Decision	Reason
Silva et al., 2018 [29] (TREND)	Include	Treatment-naïve; T&E vs monthly ranibizumab
Kertes et al., 2019 [10] (CANTREAT)	Include	Treatment-naïve; T&E vs monthly ranibizumab
Wykoff et al., 2015 [14] (TREX-AMD)	Include	Treatment-naïve; T&E vs monthly ranibizumab
Wu et al., 2025 [7] (TAEWA)	Include	Treatment-naïve; aflibercept T&E vs fixed every 8 weeks
López Gálvez et al., 2020 [13] (In-eye)	Include (pooled)	Treatment-naïve; bimonthly vs T&E (vs PRN) ranibizumab; arm-level 95% CIs allow the SE of the difference to be derived
Ohji et al., 2020 [21] (ALTAIR)	Exclude	Two T&E adjustment schedules; no fixed arm
Mitchell et al., 2021 [22] (ARIES)	Exclude	Early vs late T&E initiation; no fixed arm
Kodjikian et al., 2024 [8] (AZURE)	Exclude	Previously treated (at least 1 year of aflibercept) before randomization
Berg et al., 2015 [24] (LUCAS)	Exclude	Bevacizumab vs ranibizumab, both under T&E
Guymer et al., 2019 [23] (FLUID)	Exclude	Intensive vs relaxed fluid tolerance, both T&E
Gillies et al., 2019 [25] (RIVAL)	Exclude	Aflibercept vs ranibizumab, both under T&E
Li et al., 2023 [27] (STAR; conbercept)	Exclude	Population restricted to polypoidal choroidal vasculopathy
Jia et al., 2022 [26] (conbercept T&E vs PRN)	Exclude	Comparator was PRN, not a fixed interval
Abdin et al., 2021 [28]	Exclude	Retrospective, non-randomized
Haga et al., 2018 [9]	Awaiting classification	Randomized T&E vs every-other-month aflibercept (41 patients); treatment-naïve status not verifiable from the abstract; not pooled

TABLE 8: Eligibility decisions for all 15 candidate trials

Front Med = Frontiers in Medicine; PRN = pro re nata (as needed); T&E = treat-and-extend. CANTREAT = Canadian Treat-and-Extend Analysis Trial; LUCAS = Lucentis Compared to Avastin Study. Other trial names are used as published.

Appendix D: PRISMA 2020 flow summary

Trials identified through the targeted search (8 October 2026) and supplementary checks (7 November 2026): 15. Duplicate reports of one trial were linked; duplicate counts were not systematically captured. Screened: 15. Excluded: 9 (no fixed-interval comparator, 5; PRN comparator, 1; previously treated, 1; PCV-only, 1; non-randomized, 1). Awaiting classification: 1 (Haga et al. [9]). Eligible: 5. Included in the 12-month meta-analysis: 5. Record-level database counts are not reported because no systematic database search was performed.

Appendix E: extracted data and derivation of effect sizes

Trial	Mean change T&E / fixed (letters)	MD	SE and derivation	Injections 12 mo T&E / fixed	Other
Silva et al., 2018 [29] (TREND)	6.2 / 8.1 (LS means)	−1.88	0.995 from published 95% CI (−3.83 to 0.07); agrees with registry SEs of 0.70 per arm	8.7 (SD 2.68) / 11.1 (SD 2.43)	CSFT −169.2 / −173.3 μm
Kertes et al., 2019 [10] (CANTREAT)	8.4 (SD 11.9) / 6.0 (SD 11.9)	2.38	1.054 from published 95% CI (0.32 to 4.45) [10]; SD-based check 1.04 (n = 268 / 258)	9.4 / 11.8	24 mo: 6.8 (14.1) / 6.0 (12.6), MD 0.9 (−1.6 to 3.3) [11]; injections 17.6 / 23.5
Wykoff et al., 2015 [14] (TREX-AMD)	10.5 / 9.2	1.30	2.48 derived from two-sided p = 0.60 (only derived SE); sensitivity SE 3.3	10.1 / 13.0	24 mo: 8.7 / 10.5, P = 0.64 (no variance) [30]; injections 18.6 / 25.5
Wu et al., 2025 [7] (TAEWA)	4.1 (SD 12.3, n = 28) / 5.0 (SD 8.4, n = 12)	−0.90	3.36 from SDs and full-analysis-set sizes (taken from the trial baseline table; 40 of 44 randomized analyzed)	9.6 (SD 2.0) / 7.7 (SD 1.3)	CRT −103.7 / −131.8 μm (p = 0.4)
López Gálvez et al., 2020 [13] (In-eye)	6.4 (95% CI 2.9 to 9.8; n = 99) / 7.2 (95% CI 4.2 to 10.2; n = 103)	−0.80	2.33 from arm-level CIs (arm SEs 1.76 and 1.53; arms assumed independent)	9.3 / 7.6	PRN arm +8.0 (5.1 to 11.0), n = 104; not used

TABLE 9: Extracted data and derivation of effect sizes

BCVA = best-corrected visual acuity; CI = confidence interval; CRT = central retinal thickness; CSFT = central subfield thickness; LS = least-squares; MD = mean difference in BCVA change (letters), T&E minus fixed; mo = months; n = number of eyes analyzed; SD = standard deviation; SE = standard error; T&E = treat-and-extend. CANTREAT = Canadian Treat-and-Extend Analysis Trial. Other trial names are used as published. Data in this appendix, with the script ma.py, reproduce all pooled results.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Nawar K. Alkhalifa

Acquisition, analysis, or interpretation of data: Nawar K. Alkhalifa

Drafting of the manuscript: Nawar K. Alkhalifa

Critical review of the manuscript for important intellectual content: Nawar K. Alkhalifa

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