Monte Carlo simulation and Pareto analysis of **TREX extension rule choice** under trial-derived durability priors in neovascular AMD

Viewing TREX as a threshold search enables rational, data-informed comparison of extension rules

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BACKGROUND

- Treat-and-extend (TREX) is widely used for anti-VEGF therapy in macular disease. The injection interval is extended when disease remains stable and shortened when activity recurs.
- Despite widespread use, no principled basis exists for choosing how much to extend or shorten the interval. Longer extensions are intuitive for longer-acting agents, but how large should the increment be?
- Four-week adjustments have been shown to be safe and effective [ALTAIR study], but there is no explicit rationale for 4 weeks rather than 3, 5, or 6 weeks or longer.
- The posology for aflibercept 8 mg allows interval adjustments of 8–16 weeks after loading "at clinician discretion," but what should guide that decision?

THRESHOLD SEARCH

- We suggest these questions become clearer if TREX is viewed as a **threshold search problem.**
- After loading doses, each TREX visit tests for that unknown threshold between continued control ("dry") and recurrence ("wet"). Each eye is assumed to have a maximum dry interval (Tmax).
- Framed in this way, rules can then be compared in terms of the trade-off between speed and the risk of overshooting beyond the disease-controlling interval.

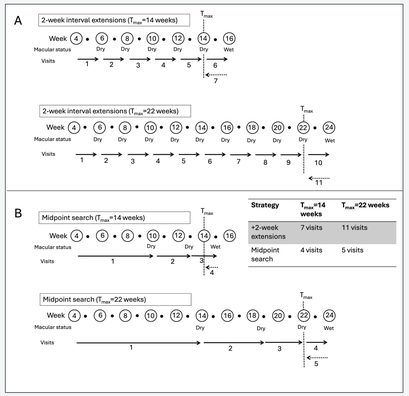
STUDY QUESTIONS

1) Can TREX interval adjustment be modelled as a threshold search problem?
2) How do commonly used extension rules compare on speed and overshoot under realistic, trial-derived durability distributions?
3) Are any rules objectively inferior — and does the optimal choice depend on agent durability?

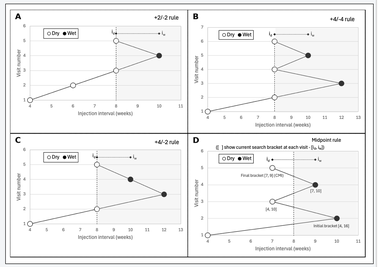
4 EXAMPLE TREX RULES COMPARED

1) +2/−2 Extend by 2 weeks if dry; shorten by 2 weeks if wet. Slow but cautious.
2) +4/−2 Extend by 4 weeks if dry; shorten in 2-week steps until dry re-established. Faster than 2-week steps.
3) +4/−4 with midpoint refinement Extend by 4 weeks if dry; step back 4 weeks after reactivation, then test once halfway between the last dry and first wet interval.
4) Midpoint (binary search) Always test halfway between the longest known dry interval and the shortest known wet interval. Narrows the uncertainty window at each visit.

Binary search is a theoretically optimal method of threshold search for speed – Figure 1 shows how a binary search compares with linear search strategies. The advantages become clearer with longer-acting agents and a wider search range.



Strategy	T_{max}=14 weeks	T_{max}=22 weeks
+2-week extensions	7 visits	11 visits
Midpoint search	4 visits	5 visits



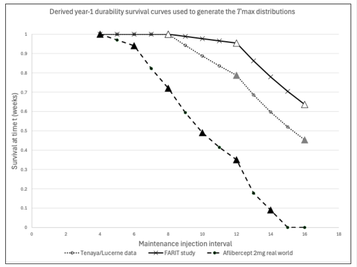
MAIN FINDING

Viewing TREX as a threshold search enables rational, data-informed comparison of extension rules

Pareto analysis identifies objectively dominated strategies and maps the trade-off between the remaining options.

METHODS

1. Enumerate deterministic TREX pathways (Tmax 4–16 weeks, 1-week grid).
2. Derive Tmax distributions from published maintenance intervals
   - TENAYA/LUCERNE — phase 3 trials nAMD faricimab
   - FARIT study – real-world cohort nAMD faricimab
   - Aflibercept 2mg — real-world cohort
3. Sample Tmax (Monte Carlo, N = 10,000)
4. Extract visits, cumulative overshoot, maximum single overshoot
5. Apply Pareto analysis (speed vs overshoot)

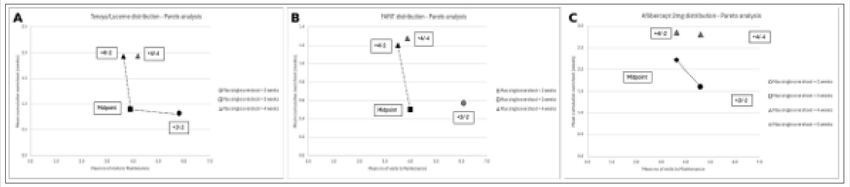


RESULTS: Key numbers from Monte Carlo simulation (N = 10,000 simulated eyes)

Durability prior	Rule	Visits to find maintenance threshold	Mean cumulative overshoot (weeks)	Maximum single overshoot (weeks)	
TENAYA/LUCERNE	**+2/-2**	5.8	0.8	2	
	+4/-2	3.6	1.9	4	
	+4/-4	**4.2**	**1.9**	**4**	**DOMINATED**
	Midpoint (binary)	3.9	0.9	3	
FARIT study	**+2/-2**	**6.1**	**0.6**	**2**	**DOMINATED**
	+4/-2	3.5	1.2	4	
	+4/-4	**3.9**	**1.3**	**4**	**DOMINATED**
	Midpoint (binary)	4	0.5	3	
Aflibercept 2mg real-world cohort	**+2/-2**	4.6	1.6	2	
	+4/-2	**3.6**	**2.8**	**4**	**DOMINATED**
	+4/-4	**4.6**	**2.8**	**4**	**DOMINATED**
	Midpoint (binary)	3.6	1.6	6	

PARETO MULTI-OBJECTIVE OPTIMISATION

Each rule is plotted as a point: mean visits to maintenance (x-axis, speed) vs mean cumulative overshoot (y-axis, safety).
Marker shape encodes maximum single overshoot.
Rules on the Pareto frontier represent genuine trade-offs; dominated rules offer no objective advantage.
The choice between non-dominated rules must be made on other grounds — such as clinical context or preference.



Pareto frontier plot: Lower-left is better. Dotted line = Pareto frontier. Dominated rules lie above and to the right of a frontier rule.

RESULTS — SUMMARY BY RULE

+4/−4

Dominated in all three analyses — another rule always matches or betters it on both speed and overshoot.
The dominance finding is most relevant when reactivation is mild.
Where reactivation is more substantial, a 4-week shortening step may remain clinically appropriate on grounds not captured by the model — the finding should not be interpreted as a blanket recommendation against larger shortening steps.

+4/−2

Fastest to maintenance across all distributions (mean 3.5–3.6 visits). Highest overshoot under faricimab priors. Best when minimising visit burden is the priority

Midpoint

Pareto-optimal under both faricimab distributions — comparable speed to +4/−2 with substantially lower overshoot.
Under aflibercept 2mg, maximum single overshoot reaches 6 weeks; not recommended when agent durability is short or high consequences of overshoot.

+2/−2

Pareto-optimal under TENAYA/LUCERNE and aflibercept 2mg priors, but dominated under FARIT — where midpoint achieves both fewer visits and lower cumulative overshoot.
Caps maximum single overshoot at 2 weeks regardless of distribution.
The safest choice when minimising overshoot is the priority, and the only rule that consistently limits maximum single overshoot across all scenarios.

CHOOSING BETWEEN NON-DOMINATED RULES

- Where multiple non-dominated rules exist, the choice depends on how overshoot and visit burden are weighted — a clinical and patient-level decision.
- Overshoot consequences are higher when: eye is only-seeing, disease is aggressive, prior reactivation was rapid, or the patient is anxious about recurrence → favour +2/−2.
- Visit burden matters more when: treatment burden is high, patient has limited mobility, or the agent is long-acting with low reactivation risk → favour +4/−2 or Midpoint.

The Pareto framework identifies which options are rational; clinical context and patient preference determine which Pareto optimal rule to choose.

LIMITATIONS

- Tmax modelled as fixed; in practice this may change over time.
- Durability priors were derived from year-1 maintenance intervals as a pragmatic proxy for Tmax.
- Real-world durability distributions may differ to those seen in clinical trials.
- Only four rules compared — hybrid or clinician-modified strategies not modelled.

CONCLUSIONS

- Viewing TREX as a threshold search provides a principled framework for choosing/comparing/justifying extension rules.
- For longer-acting agents, midpoint achieves near-optimal efficiency with substantially better overshoot control than 4-week extension rules.
- For shorter-acting agents, +2/−2 is safest — maximum single overshoot capped at 2 weeks.
- Rule choice should reflect agent durability, disease context, and patient preference.

FUTURE DIRECTIONS

Real-world priors: Local and national maintenance interval data would improve rule selection beyond trial-derived estimates.
Personalised prediction: OCT biomarkers and early treatment response may predict individual Tmax, enabling personalised rule choice before the search begins.
Longer-acting agents: Extension of analysis to the 4–24-week range for aflibercept 8mg.
Prospective validation: Head-to-head rule comparison with pre-specified efficiency and overshoot endpoints