



Webinar Session

Action Limits as an Early Warning System within a QTL Monitoring Strategy

PHUSE Working Group QTL Thresholds
September 1, 2026



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Welcome

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2-Session Webinar on QTL Monitoring

Webinar 1: Setting the QTL Threshold (23 June 2026)

Webinar 2: Action Limits (1 September 2026)

Presentation

Round Table

Q&A Session – Put your questions in the Q&A section



QTL Threshold Working Group

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Agenda Topics

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- **Building on QTL Thresholds**
 - Why Action Limits Matter Operationally
 - Action Limits as Early-Warning Signals
 - Operational and Statistical Design Considerations
- **Action Limit Approaches During Trial Conduct**
- **Interpreting Signals to Support Timely Mitigation**



Action Limits: Building on QTL Thresholds

Webinar 1

Setting the QTL Threshold

QTL parameters

Threshold-setting considerations

Four doors that inform threshold decisions



Webinar 2

Enhancing QTL Monitoring

How Action Limits complement QTL thresholds

How earlier signals support investigation

How operational and statistical perspectives work together

QTL threshold = boundary | Action Limit = early-warning signal



Why Action Limits Matter Operationally

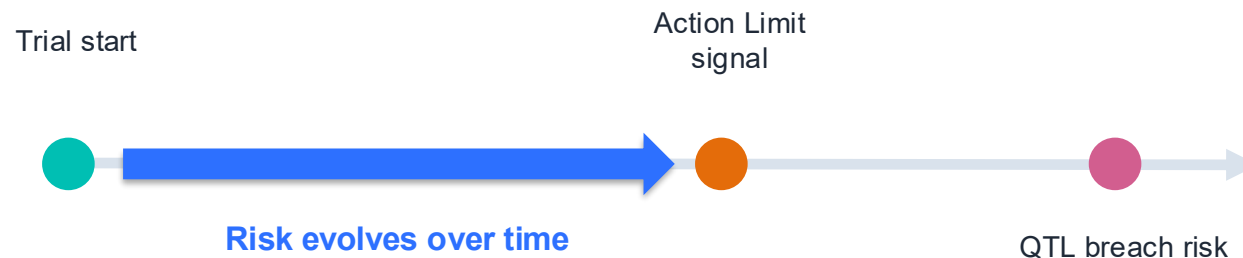
QTL thresholds define the boundary of acceptable trial-level quality risk.

The operational gap

Some QTL parameters are most informative late in trial conduct.

A QTL breach may leave limited time to mitigate.

Teams need earlier signals to allow time to investigate, interpret, and act.



Action Limits provide earlier visibility to emerging risks, enabling timely investigation and mitigation before risk increases.



Action Limits Are Not Mini-QTLs

View Action Limits as a structured prompt for earlier review, not as a replacement for QTLs.

Signal

An early indication that a risk pattern may be evolving differently than expected.

Assessment

Evaluation of the observed pattern using clinical, operational, and statistical context.

Response

Determine whether to mitigate, escalate, continue monitoring, or gather additional information.

Action Limit breach ≠ automatic escalation or conclusion that trial quality is compromised.



From Operational Question to Statistical Design

Operational question

What emerging risk are we trying to detect early enough to act?



Statistical design question

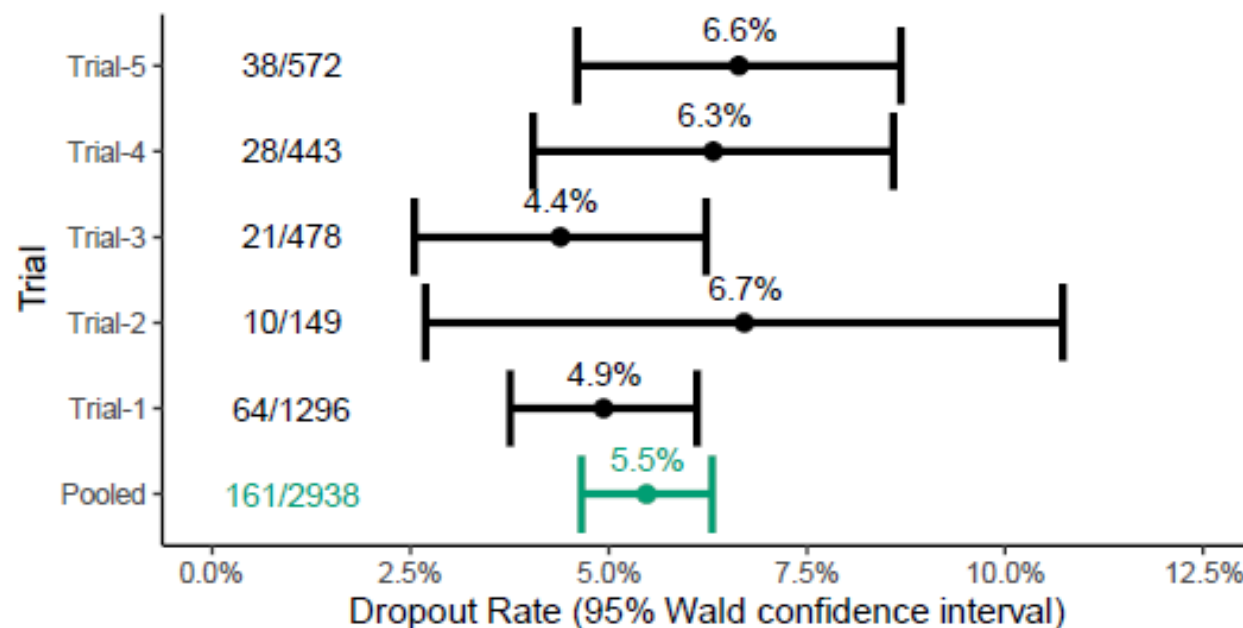
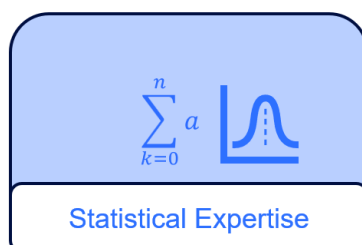
How should the Action Limit reflect expected risk evolution and available information?

Shared goal: timely, evidence-informed trial oversight.



The Trial We Left In June

Phase II · plaque psoriasis · 200 participants · 12 weeks treatment · 12 weeks recruitment



CtQ FACTOR

Completeness of primary endpoint data

THE RISK

Excess participant discontinuations weaken data reliability

CRITICAL DATA

Primary endpoint data

QTL PARAMETER

Dropout rate



Where the QTL Threshold Came From

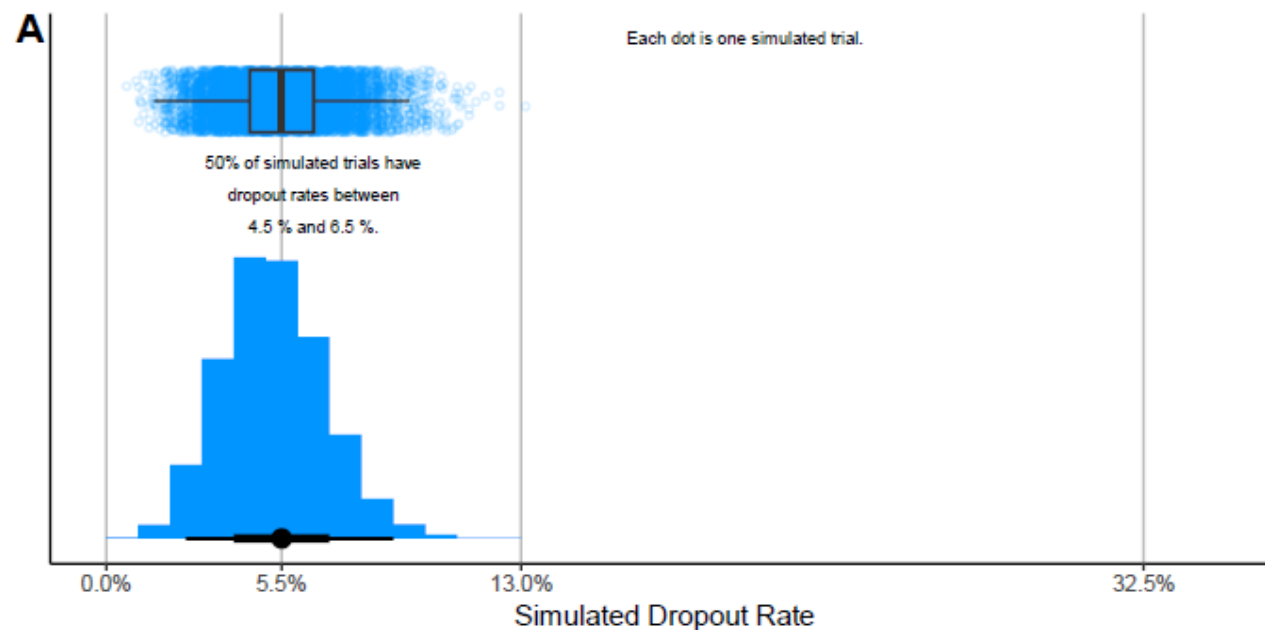


Figure 3A, Keller et al. 2024

The Maximum

None of the 10,000 simulated trials exceeded

13%

THE TOP OF THE BOX

Three quarters of normal trials stay below

6.5%



Be Mindful of The Denominator

EARLY IN THE TRIAL

2 of 40 enrolled

5.0%

ONE MORE LEAVES

3 of 40 enrolled

7.5%

END OF TRIAL

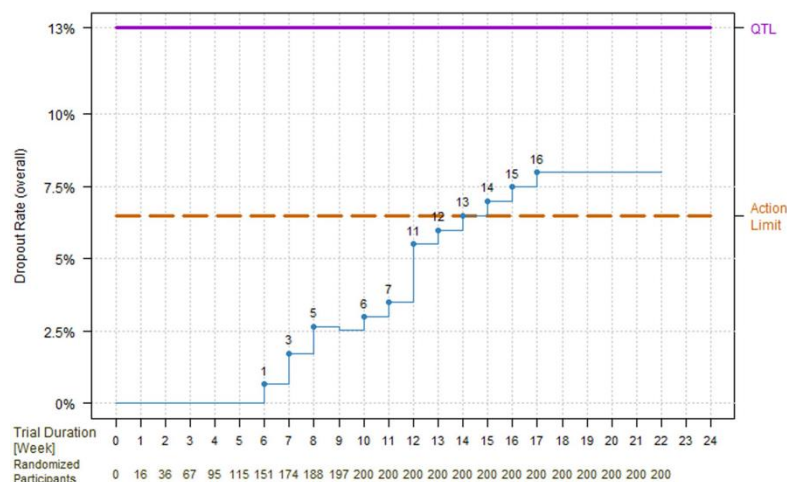
26 of 200 enrolled

13.0%



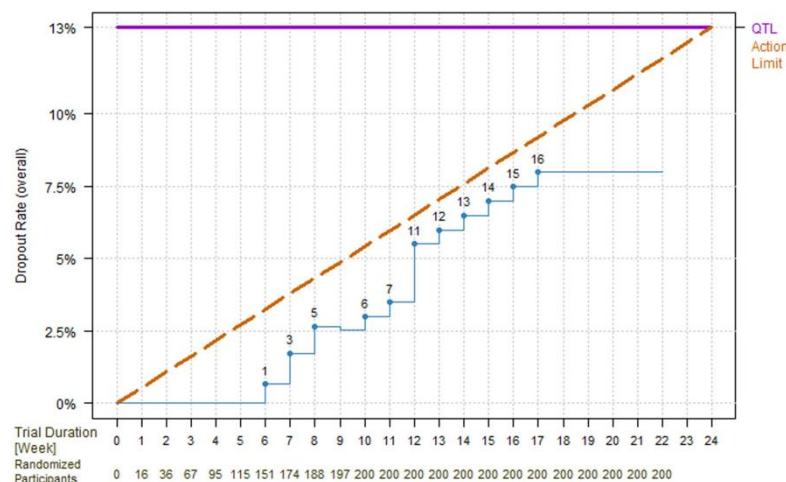
How the Action Limits Interact with the Trial

CONSTANT



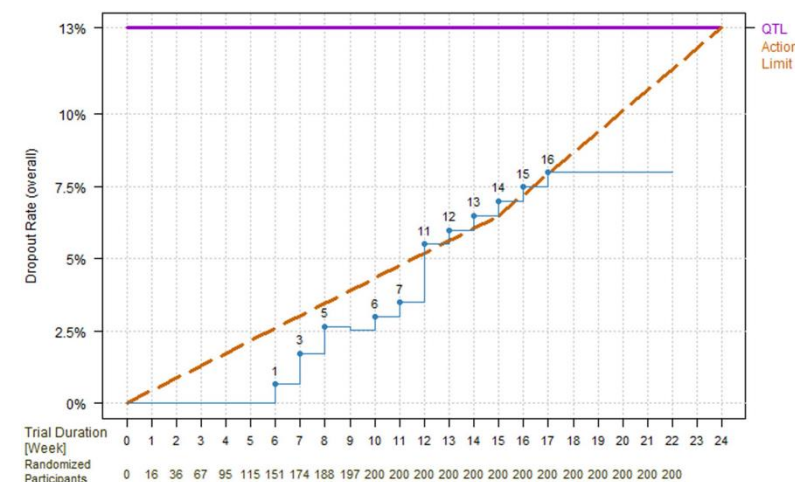
Signal in week 14

INCREASING



No signal at all

EXPECTED PATTERN



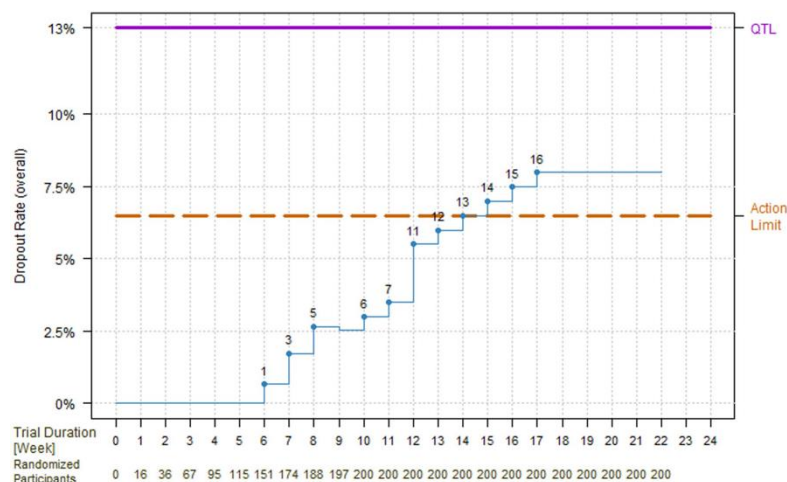
Signal in week 12

Figures 3, 4 and 5, van Borrendam et al. 2026



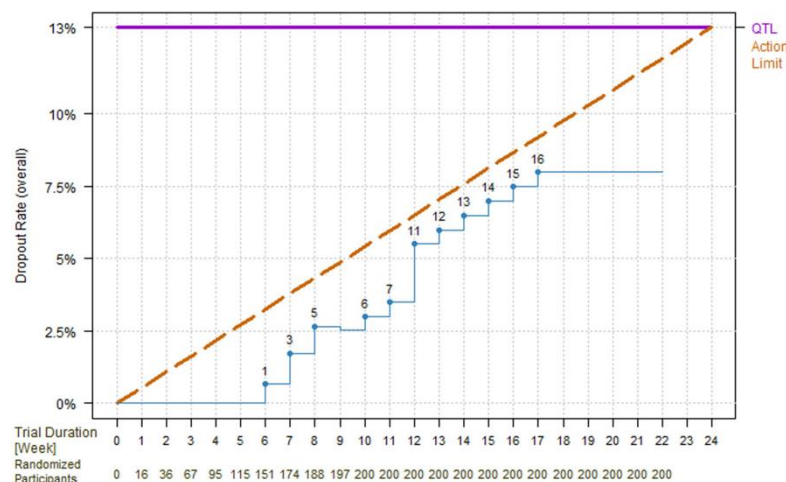
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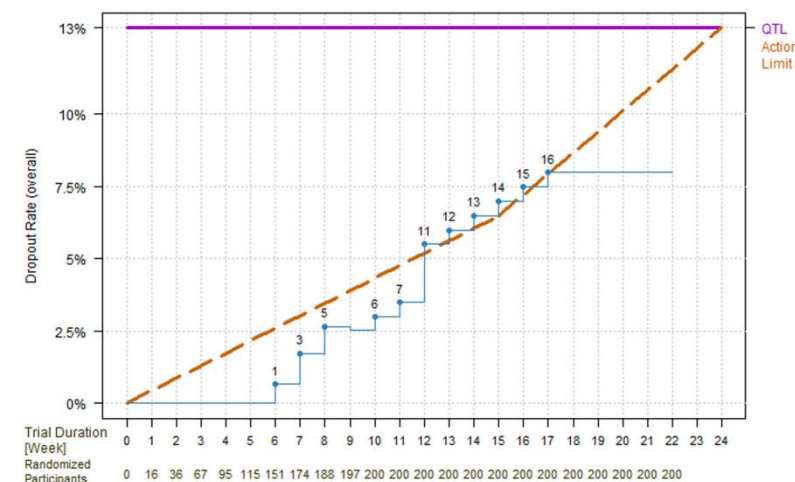
Signal in week 14

INCREASING



No signal at all

EXPECTED PATTERN



Signal in week 12

Figures 3, 4 and 5, van Borrendam et al. 2026

Value comes from defining assumptions before the trial begins



What Action Limits Add to QTL Monitoring

- 1 Detect evolving risk patterns earlier
- 2 Investigate before trial quality may be impacted
- 3 Interpret signals using operational, clinical, and statistical context
- 4 Support timely, targeted mitigation
- 5 Strengthen proactive QTL monitoring

The strongest use of Action Limits is when the signal is interpreted in context.



The Core Philosophy

1



A QTL threshold defines the boundary of acceptable trial-level quality risk.

2



An Action Limit provides an earlier signal that risk may be evolving differently than expected.

3



Effective QTL monitoring requires both statistical and clinical/operational judgment.

Action Limits are not just another threshold. They are a mechanism to create time for better decisions.

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THANK YOU!