Paper AR08

Efficient Positioning of QTL and Secondary Limit Thresholds in a Clinical Trial Risk-based Monitoring

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Abstract

The paper discusses a novel methodology for efficiently positioning Quality Tolerance Limits (QTL) and Secondary Limit (SL) thresholds in clinical trials, focusing on risk-based monitoring (RBM) and risk-based quality management (RBQM) — detailed methodology presented in [1,2].

Introduction

A clinical trial holds many potential risks that could jeopardize a company's multimillion-dollar drug development investment. The increasing complexity of clinical trials compounds these challenges. Therefore, comprehensive risk planning, including an efficient risk mitigation strategy, is essential for clinical trial planning and execution.

The typical risk planning process is cyclical and includes four interconnected steps: identification of potential risks, risk assessment, risk response planning, and risk monitoring.

Risk mitigation strategy planning

Risk response planning aims to reduce risk. Several options could be considered: risk avoidance (an alternative approach that does not include a particular risk), risk prevention, risk transfer (e.g., insurance to cover patients' safety), risk acceptance, and risk mitigation. The paper addresses clinical trial risk mitigation planning.

Risk mitigation planning includes three interconnected components:

1. Development of a risk mitigation strategy [1].
    a. Derivation of a contingency budget.
    b. Efficient contingency budget allocation across risks.
    c. Efficient selection of a risk mitigation option for each risk, assuming some risks may be associated with several mutually exclusive risk mitigation options (e.g., backup sites in country A or B).
    d. Alignment of a contingency budget and risk tolerance

2. Establishment of the operational risk mitigation rules
3. Align the mitigation strategy and the operational risk mitigation rules [2].

The modeling technique to address risk mitigation strategy planning was presented in [1]. The method assumes efficient risk mitigation is possible if sufficient contingency resources are allocated. However, efficient allocation of contingency resources does not guarantee flawless risk mitigation process execution. The process should be subject to operational rules that keep multiple Risk Parameters (RP) within an acceptable range to minimize risk exposure during clinical trial execution [2]. The operational rules are derivatives of the risk mitigation strategy and are defined by thresholds.

The critical issue in RBM is how to efficiently position QTL and SL thresholds and align them with risk assessment and mitigation costs.

The Methodology

The methodology presented in Figure 1 is based on interconnected strategic and operational risk planning mathematical models. It includes three steps: (1) strategic risk planning (Risk Optimizer), (2) operational risk planning (Risk Simulator, and (3) alignment of strategic and operational risk planning.

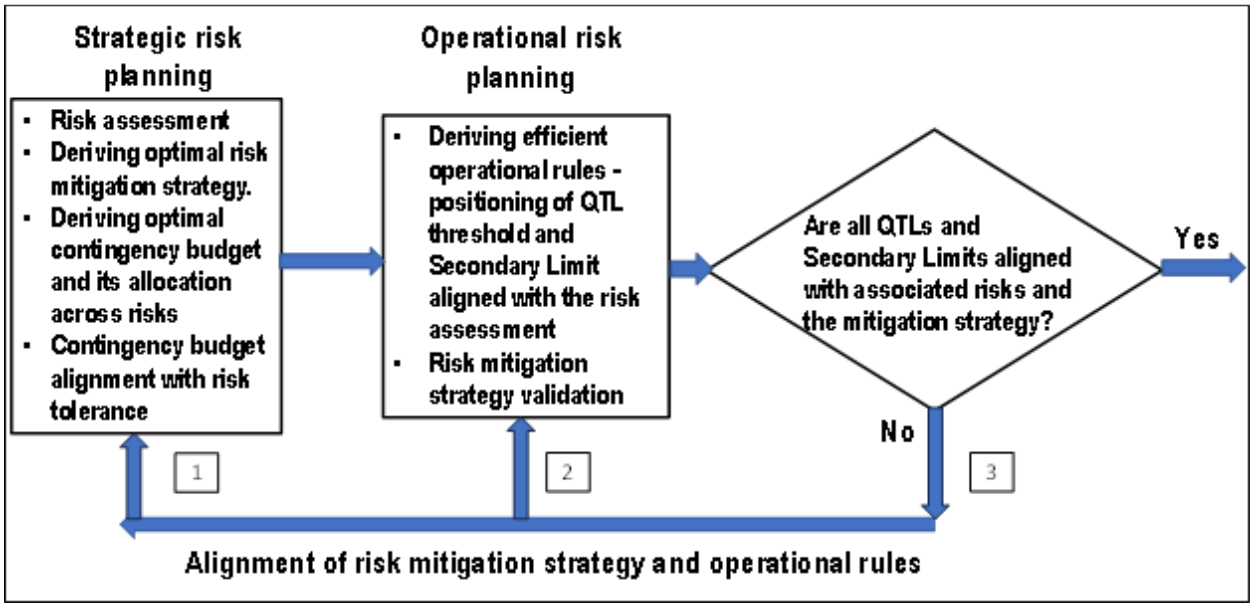


Figure 1. The risk mitigation planning methodology.

Strategic risk planning (block 1) includes (1) risk assessment, (2) the optimal risk mitigation strategy planning (selection of an efficient mitigation option for each risk), (3) the optimal contingency budget derivation and its allocation across risks, and (4) contingency budget alignment with risk tolerance [1]. The outcome of the strategic risk planning stage is (a) residual risk and (b) allocated resources to mitigate each risk.

Operational risk planning (block 2) goals include deriving efficient operational rules, i.e., positioning QTL and SL thresholds aligned with risk assessment and mitigation resources.

Alignment of strategic and operational risk planning (block 3) coordinates modeling results from blocks 1 and 2. For example, the QTL threshold may not be aligned with risk, or contingency resources could

differ from outcomes from optimization and simulation models due to high uncertainty in data and risk assessments.

A simplified example/analogy explains the proposed methodology.

Example: Each modern car has a fuel indicator. Suppose the fuel level in the tank reaches a low-level point where the indicator flashes. The responsible driver should stop at the nearest gas station if they have sufficient money to fill the tank to mitigate the risk of an empty tank. The risk of an empty tank in the middle of the road is considered critical and has a significant negative impact.

The driver may have several mitigation options. They are: (1) filling up the tank at the nearest gas station; (2) if fuel is expensive at the nearest gas station, they can partially fill the tank enough to get to a cheaper station; (3) passing the current gas station and fill the tank at a cheaper station, but the risk of an empty tank will increase.

If the driver faces two risks (e.g., an empty tank and a potential flat tire), they must allocate money to mitigate them - a potential tire repair/replacement and filling up the tank. Also, planned money allocation may not correspond with actual spending due to uncertainty on the road.

This analogy can be applied to the clinical trial risk management process.

RP is associated with the fuel amount in the tank, e.g., "*% or number of randomized study participants who do not meet exclusion/inclusion criteria "[4];* QTL is associated with an empty tank or with a minimum % of patients meeting exclusion/inclusion criteria (e.g., 80%), and a fuel indicator is associated with SL (e.g., 85%) where the risk mitigation should start.

Assumptions:

(1) all analyzed risks are mitigated.

(2) a contingency budget is limited.

(3) each mitigation action requires resources.

Models – Risk Optimizer and Risk Simulator

1. Optimal risk mitigation strategy – Risk Optimizer [1]

An efficient risk mitigation strategy should be able to address the following questions.

a) How to derive a contingency budget that is aligned with risk?
b) How can a contingency budget be optimally allocated across risks?
c) How can the risk mitigation strategy for a clinical trial be optimized?
d) How can a contingency budget, mitigation strategy, clinical trial risk capacity, risk appetite, and risk tolerance be aligned [1]?

The problem statement

- In a clinical trial, high and medium operational risks should be mitigated.
- Each risk may have several mutually exclusive mitigation options. For example, backup clinical sites could be in countries X, Y, or both (Table 1).

Input and output data

Input								Output
# Risk	#	Likelihood **(L)**	Impact **(I)**	Total Score **(LxI)**	Mitigation cost –**(M)**	Probability **(P)**	Risk-adjusted mitigation cost (M**xP**)	Selected the mitigation option
	A	B	C	D	E	F	G	H
Risk	1							
Mitigation options	1.1 (no mitigation)							X
	1.2							
Risk	2							
Mitigation options	2.1 (no mitigation)							
	2.2							
	2.3							X

Table 1. Framework for the input data and modeling results (output).
Legend. *Column A presents risk and potential risk mitigation options. For example, Risk 1 has two options – 1.1 no mitigation and 1.2 - mitigation. Risk 2 has three mitigation options – 2.1 (no mitigation). Options 2.2 and 2.3 include mitigation. Output - X – selected mitigation option [1]. Option 1.1 was selected, and option 2.3 was selected.*

Likelihood score - L	1	2	3	4	5
Qual. Rating	Very low	Low	Medium	High	Very high
Average, risk/probability P, %	10	25	50	75	90
Range, risk/probability (P_{min}, P_{max}), %	5-15	15-35	35-65	65-85	85-95

Table 2. Likelihood score and probability (risk).
Legend. The likelihood score $\boldsymbol{L_i}$ *scaled from j = (1,5) is a surrogate for an average risk/probability* $\boldsymbol{P_i} =$ $(0,1)$ *(Li ↔ Pi) or the range of probabilities presented in Table 1. For example, due to assessment subjectivity, a score of five corresponds to "a very high" risk/probability of 90% or within the 85% - 95% range.*

Impact - I	1	2	3	4	5
Rating	Very low	Low	Medium	High	Very high

Table 3. Impact score

Contingency budget – **B**

The optimization model. The model selects an optimal risk mitigation plan, allocating a contingency budget across risks and minimizing the Total Normalized Risk Score (TNRS – a sum of risk scores divided by a total number of mitigated risks) [1] for the entire portfolio of clinical trial risks. It also allocates limited contingency resources across risks, selecting an optimal mitigation option for each risk.

$$TNRS = \frac{\sum_i (Score\ risk(i))}{\#\ mitigated\ risks} \quad (1)$$

The score risk (or average impact [1] for risk (i) is

Score risk(i) = Impact(i) x Likelihood(i) [1] (2)

2. RBM risk simulator.

The RBM simulator mimics RP dynamics for each mitigated risk. It was developed to validate the risk mitigation strategy and establish operational rules.

An illustration of the RP dynamic is presented in Figure 2.

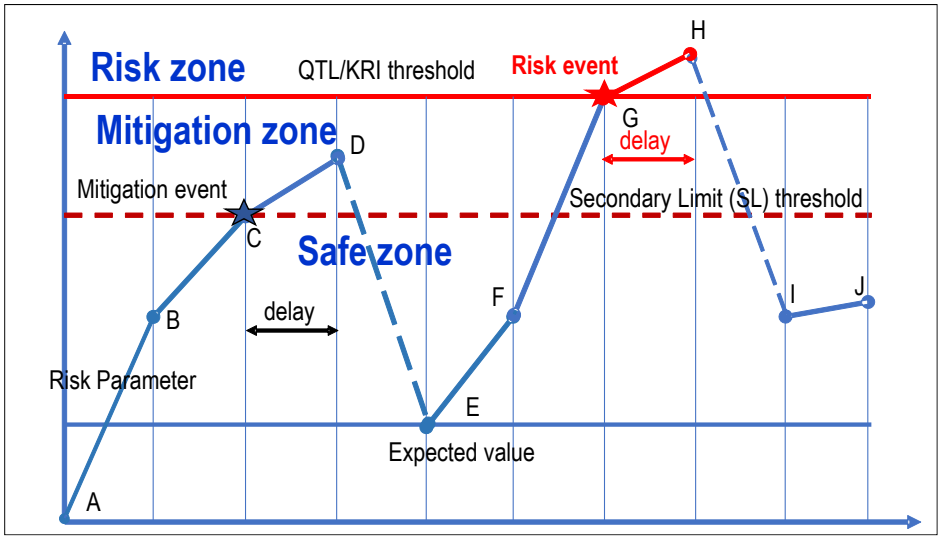


Figure 2. Illustration of RP dynamics.

Legend: X-axis—time, Y-axis—the dynamic of an RP parameter.

The RP space includes several horizontal lines: The "expected value" line for the RP, the SL line, and the QTL line. The space between the SL and the QTL is the mitigation zone, and the space between the SL and the X-axis is a safe zone.

The RP dynamics can be described as follows. When the RP reaches or exceeds the SL line (point C – mitigation event), the mitigation should start according to the mitigation plan with a delay—the longer the delay, the closer an RP is to the QTL threshold (point D) and the early warning effect may have a

lower value. The mitigation plan may include training, additional site visits, teleconferencing calls, activating backup sites, and other actions depending on the risk, time, and costs = $\mathbf{C_{DE}}$. As a result of the mitigation, the RP value is reduced to the expected value (point E)[1], consuming contingency resources. Then, for illustration purposes, the rise of RP is very steep and may reach (or exceed) the QTL line (point G - risk event). Due to the delay between risk occurrence and the mitigation start (cycle time), the mitigation can only start at point H, making the potential impact bigger. The mitigation costs (H-I) include planned $\mathbf{C_{HI}}$ and unplanned costs - $\mathbf{\Delta C_{HI}}$ (the fuel indicator example above; $\mathbf{\Delta C_{HI}}$ corresponds to wasting time and higher fuel costs). Also, the reduction of **RP** may not reach the Expected Value level due to insufficient contingency funds. The total mitigation costs are -

$$\mathbf{C_{mit} = C_{DE} + C_{HI} + \Delta C_{HI}} \quad (5)$$

The model outcome includes two essential parameters.

1. Risk as the probability of RP reaching QTL level and described with Equations (4) and (5)

The risk - R in the Monte Carlo simulation model is calculated as:

$$R = \frac{\sum_n E_n}{N} \quad (6)$$

N – number of simulation cycles, n – simulation cycle where the risk event occurs. $1 \le n \le N$.

$E_n = \{1\text{- risk event occurs, i.e., } RP_n(t) > QTL; 0 - \text{otherwise}\}$

t – time, T – clinical trial duration. $0 \le t \le T$.

2. Average mitigation costs

$$C_{mit,av} = \frac{\sum_n C_{mit,n}}{N} \quad (7)$$

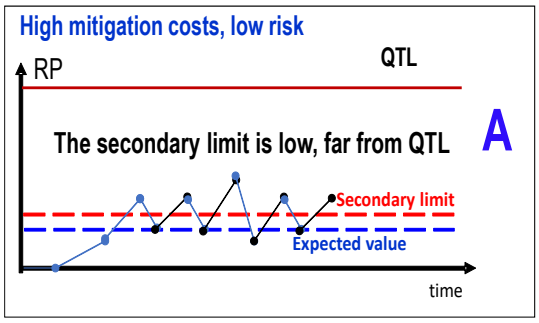
$C_{mit,n}$ – mitigation costs in the n-th simulation cycle.

How can QTL and SL thresholds be positioned efficiently?

The QTL threshold positioning. If the QTL threshold is too high, the risk event could be missed, and a "fake" risk event will be reported if the QTL threshold is too low. Therefore, the QTL threshold position should be aligned with the risk assessment after the mitigation in the Risk Optimizer. For example, if a likelihood score before the mitigation is three and after the mitigation is two, the "right" QTL threshold position should correspond with the risk within a range (15-35%) (Table 2) [1].

The SL positioning (QTL level is fixed). Suppose the SL threshold is low (far from the QTL threshold), as presented in Figure 3A. In that case, the RP often crosses the SL threshold, triggering mitigation activities. The mitigation costs are high, but there is a low risk of reaching or exceeding QTL. If the SL threshold is high (close to the QTL threshold), the RP may cross the QTL level more often to increase the risk (Figure 3B), but mitigation costs will be low.

[1] As an example



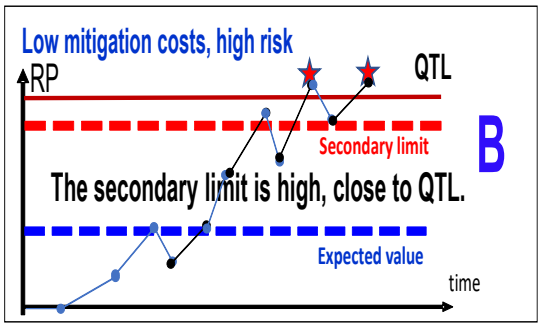


Figure 3A. Low SL threshold.

Figure 3B. High SL threshold.

Therefore, the SL threshold position should be aligned with the mitigation costs.

Suppose the risk and mitigation costs generated by the RBM simulator are not aligned with the Risk Optimizer input data presented in Tables 1-3. In that case, the input data should be reviewed and corrected (Figure 1, block #3), and the models should be rerun with corrected data.

Case study [2]

Problem statement

- Ten significant risks were identified and assessed in a clinical trial to be mitigated.
- Each risk is characterized by its likelihood and impact.
- Each risk may have several mutually exclusive mitigation options.
- Likelihood, impact, and mitigation costs are associated with each mitigation option.
- The contingency budget is limited.

Deriving efficient risk operational rules

The goal is to efficiently position QTL and SL thresholds for each risk presented in Table 4 to be aligned with risk assessment and contingency resources.

The problem is delineated in two interconnected sub-problems.

(1). Deriving an optimal risk mitigation strategy (Figure 1) [1] involves selecting the mitigation option for each risk and deriving the corresponding residual risk (Risk Optimizer). For example, for risk #1, mitigation option 1.1 was selected after the modeling (Table 4, column H). It means that the residual risk = 2 (the probability of occurrence is within the range of 15-35%) (Table 2), and risk-adjusted mitigation costs = 3.75.

# Risk	Likelihood, L	Impact, I	Total Score, LxI	Mitigation cost, M	Probability, P	Risk-adjusted Mitigation costs, MxP	Selected Mitigation options
A	B	C	D	E	F	G	H
1	3	4	12	0	0.5	0	0
1.1	2	4	8	15	0.25	3.75	**1**
1.2	2	4	8	45	0.25	11.25	0
1.3	1	4	4	120	0.1	12	0
2	4	4	16	0	0.9	0	0
2.1	3	4	12	80	0.5	40	0
2.2	2	4	8	105	0.4	42	0
2.3	2	4	8	180	0.25	45	**1**
3	3	5	15	0	0.5	0	0
3.1	3	5	15	60	0.5	30	**1**
3.2	2	5	10	120	0.4	48	0
3.3	1	5	5	165	0.4	66	0
4	3	4	12	0	0.5	0	0
4.1	2	4	8	96	0.3	28.8	**1**
5	5	4	20	0	0.9	0	0
5.1	3	4	12	50	0.5	25	**1**
5.2	2	4	8	132	0.25	33	0
5.3	2	4	8	150	0.25	37.5	0
5.4	2	4	8	180	0.25	45	0
6	4	4	16	0	0.75	0	0
6.1	2	4	8	69	0.25	17.25	**1**
7	4	5	20	0	0.75	0	0
7.1	1	5	5	90	0.1	9	**1**
8	4	4	16	0	0.75	0	0
8.1	1	4	4	150	0.1	15	**1**
9	3	4	12	0	0.5	0	0
9.1	1	4	4	135	0.1	13.5	**1**
10	4	4	16	0	0.5	0	0
10.1	2	4	8	150	0.25	37.5	**1**

Table 4. Input data for the case study (data is random).

Legend. *Example. Risk#1 has three mutually exclusive options: (1) no mitigation, (1.1), (1.2), and (1.3) with reduced likelihood. For the selected mitigation option 1.1, mitigation costs are 15, and risk-adjusted mitigation costs are 3.75.*

(2). Deriving efficient operational rules – positioning QTL and SL thresholds for each risk aligned with risk assessment and contingency resources (RBM Simulator).

If one or both parameters (QTL and SL thresholds) are not aligned, risk assessment and mitigation resources are corrected (Figure 1, block #3). Then, the recalculation of models (1) and (2) for the adjusted thresholds (Figure 1) is necessary. Aligning QTL thresholds with risk assessment and mitigation resources may require up to four modeling iterations.

Efficient positioning of QTL and SL thresholds

The RBM simulator aims to validate the efficiency of selected risk mitigation strategy and derive efficient operational rules.

Input data

a. For each risk, a range of acceptable QTL thresholds based on historical trials, experience, and expert opinion is similar to [14].

$$\mathbf{QTL_{min} \leq QTL \leq QTL_{max}.} \quad (8)$$

Some QTL thresholds are fixed, e.g., "*% or number of randomized study participants who do not meet exclusion/inclusion criteria "[4].* In this case, only the SL threshold should be positioned.

b. For the risk assessment range, see Table 2.

c. Risk parameter deviation (min, max) $\mathbf{RP(t)_{min} \leq RP(t) \leq RP(t)_{max}}$

d. Parameter reduction due to the mitigation (min, max)

$\mathbf{\Delta RPM(t)_{min} \leq \Delta RPM(t) \leq \Delta RPM(t)_{max}}$

e. Cycle time to resolve the mitigation or risk signal (delay)

f. Cost per mitigation action (min, max)

Modeling results

1. Efficient QTL threshold positioning.

Let's consider the positioning of the QTL threshold for risk 1. Risk 1 was mitigated as part of the risk mitigation strategy for the entire portfolio of risks (Table 4) using the model presented in [1]. Mitigation option 1.1 was selected. The risk likelihood was reduced from = 3 to = 2 or, on average, from 0.5 to 0.25, with a range of 0.15-0.35 (Table 2).

Simulation experiments were conducted for the QTL threshold range (0.12 – 0.19) and SL range from 0.06 to the level of the QTL threshold. The goal is to find a combination of QTL and SL thresholds aligned with the clinical trial risk and contingency resources.

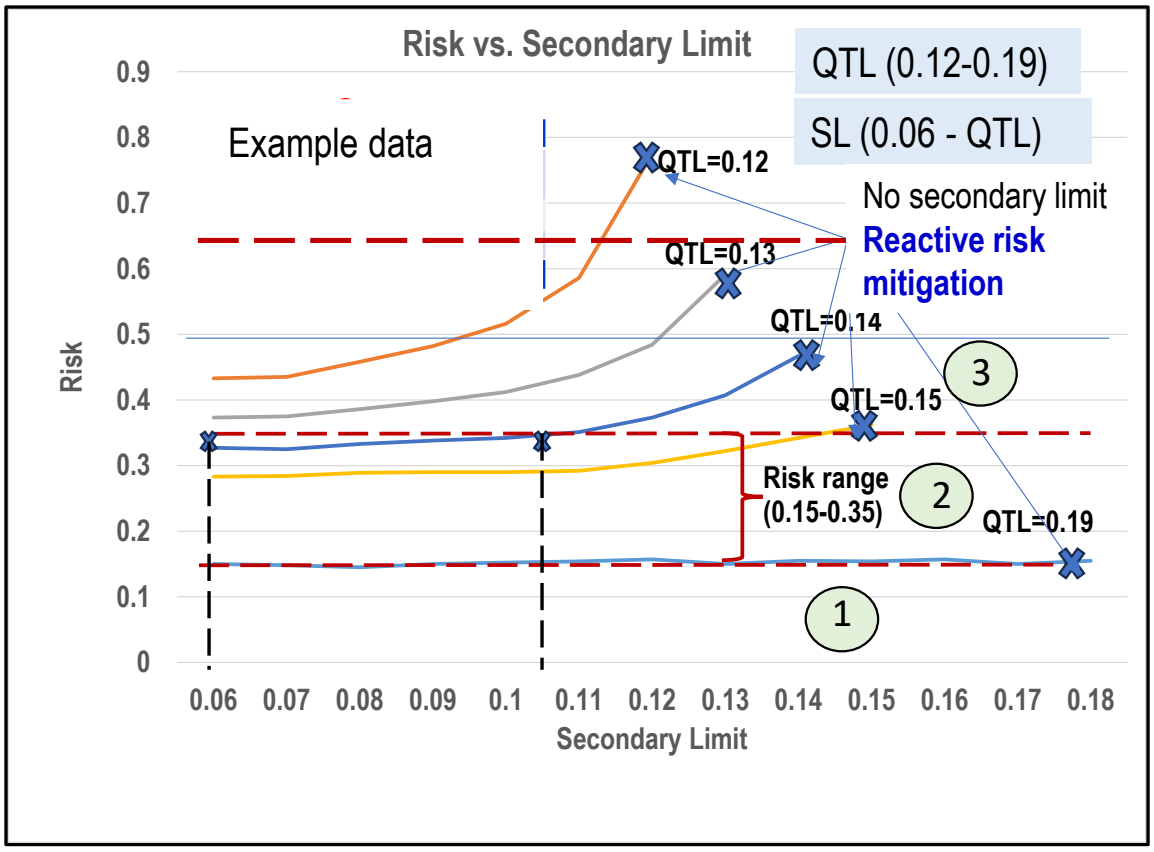


Figure 4. Clinical trial risk vs. SL for different QTL values.

***Legend**. The horizontal lines are boundaries between risk zones. Example: Zone #2 corresponds to the risk range of 0.15 – 0.35 (Table 2).*

If the QTL threshold is 0.12, the risk is outside the required likelihood range of 0.15-0.35 for all SLs from 0.06 to 0.12.

Increasing the QTL threshold reduces the risk. If QTL = 0.15, the risk for all SLs is within the range (0.15-0.35). The points marked X correspond to SL threshold absence (reactive risk mitigation). Results in Figure 4 indicate that without SL, the risk of reaching or exceeding the QTL threshold is higher than with SL (proactive vs. reactive risk mitigation).

2. Efficient Secondary Limit (SL) threshold positioning

Simulation experiments were conducted for a fixed QTL threshold = 0.15 and variable SL. They are presented in Figure 5, capturing SL vs. risk-adjusted mitigation costs according to the observations in Figures 3A and 3B.

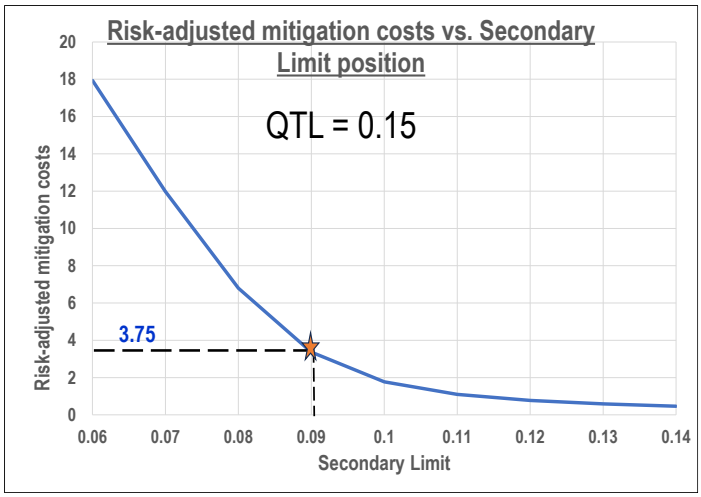


Figure 5. Risk-adjusted mitigation costs vs. Secondary Limit position.

The graph indicates that the lower the SL, the higher the mitigation costs. Selected risk mitigation option 1.1 for risk 1 requires a risk-adjusted mitigation cost of 3.75, corresponding to SL = 0.09, QTL = 0.15, and risk =0.29 (within the range 0.15-0.35, Figure 4).

Optimization and simulation models must be recalculated with updated data if modeling results (risk and mitigation costs) are not aligned with established QTL and SL limits (Figure 1, block #3). This process requires an expert opinion, especially in the risk reassessment.

Cycle time response to the risk signal analysis. One of the model's critical parameters is the "cycle time response to the risk signal." A benchmarking study [16] showed that the average time to respond to the risk signal was around 35 days. Is it too long, too short, or just right? It seems intuitive that the cycle time should be as little as possible because an RP could continue to grow after crossing the SL threshold and potentially jeopardize the integrity of trial results.

The graph in Figure 6 indicates that the longer the delay between the risk signal and the response, the higher the probability of a risk event. Without response after crossing the SL threshold, the RP will continue increasing until the start of the mitigation.

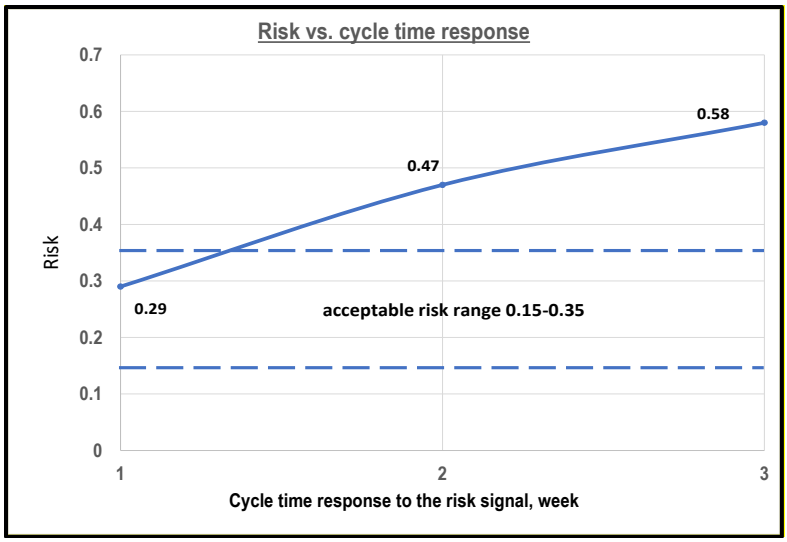


Figure 6. Risk vs. cycle time response to the risk signal.

According to the graph in Figure 6, the risk = 0.29 is within an acceptable range (0.15-0.35) only if the delay in response to the risk signal is about a week. If the mitigation postponement equals two weeks, the risk becomes = 0.47; for a three-week delay, the risk becomes = 0.58. If the delay cannot be reduced to the required value, then the only option is to raise the QTL threshold to stay within risk limits.

Conclusion

The paper presents a technique for efficiently positioning QTL and Secondary Limit thresholds. The technique advantages:

- It is clinical trial-specific.
- It aligns thresholds with risk assessment and contingency resources.
- Small and medium companies can use it without utilizing substantial historical data.
- The thresholds can be adjusted during clinical trial execution.

References:

1. Shnaydman, V. Efficient Risk Mitigation Planning for a Clinical Trial. Therapeutic Innovation & Regulatory Science (2023) 57:717–727
2. Shnaydman, V. Efficient Positioning of QTL and Secondary Limit Thresholds in a Clinical Trial Risk-Based Monitoring. Therapeutic Innovation & Regulatory Science. **59**, 173–183 (2025).

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