

Efficient positioning of QTL and Secondary Limit thresholds

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Eternal RBM/RBQM questions

1. How do you position QTL and secondary limit thresholds?

1. Historical data – statistical processing
2. Benchmarking
3. Gut feelings
4. Modeling

2. Do QTL and secondary limit thresholds relate to risk mitigation?

3. What do you think about risk detectability?

The Problem Statement

- ✓ Risks in clinical trials related to patients' enrollment, site selection, protocol amendments, clinical supply stock-out, biological sample handling, and many others. Poor risk planning can potentially delay or even compromise trial results.
- ✓ The ongoing risk planning process includes multiple steps, such as identifying potential risks, analyzing and quantifying them, and developing an effective risk mitigation strategy based on available contingency resources and efficient operational rules.

Critical questions need to be answered.

1. What would be the best mitigation option for each risk?
2. How can a contingency budget across risks be allocated efficiently?
3. How can QTL and the Secondary Limit be positioned efficiently for each risk before a trial starts?



Definitions*

A risk parameter (RP) is a quantitative measure that helps assess the level of risk.

Example: % or number of study participants randomized who do not meet exclusion/inclusion criteria

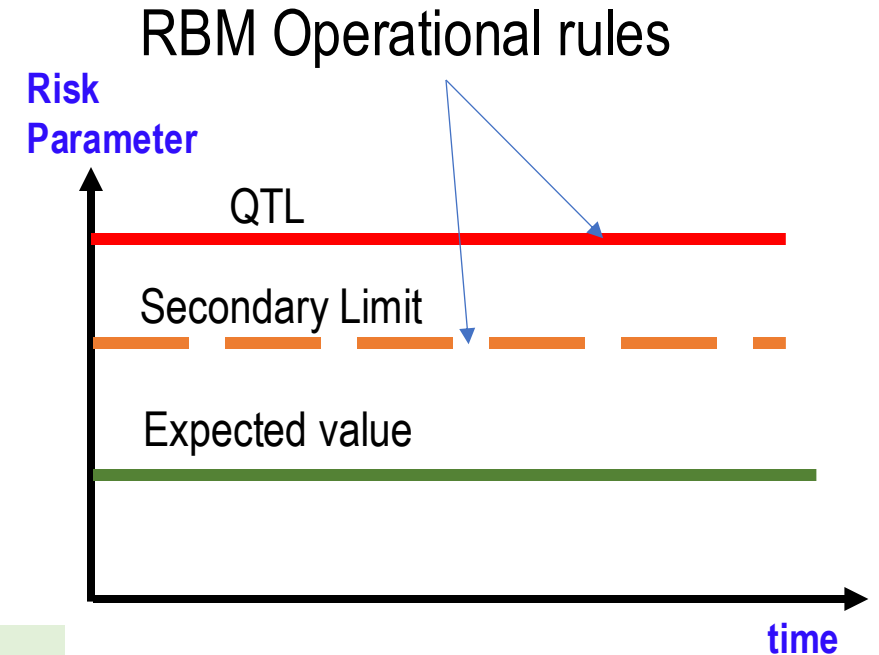
A Quality Tolerance Limit (QTL) is a **predefined** threshold associated with the RP. If the RP reaches the QTL, the safety and reliability of trial results can be severely impacted. The QTL threshold is trial and risk-specific.

Secondary Limit – a threshold associated with the RP that **triggers mitigation activities** to prevent the indicator from reaching the QTL and avoiding risk events.

Risk event – occurs when risk parameter reaches or exceeds QTL threshold

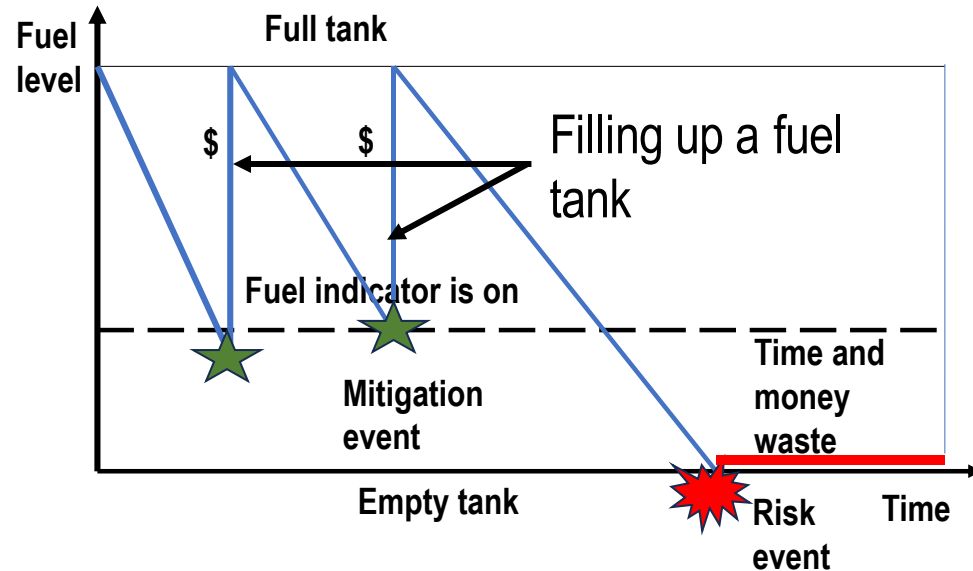
Mitigation event – risk parameter reaches or exceeds Secondary Limit threshold

- Assumption: $(QTL_{min} \leq QTL \leq QTL_{max})$.
- Some QTLs are fixed, e.g., maximum % or number of study participants randomized who do not meet exclusion/inclusion criteria



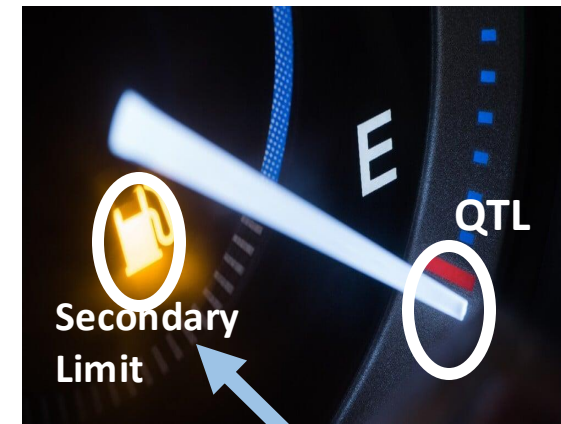
Real-life analogy – Risk Mitigation of the Empty Gas Tank

- During a long trip, a driver has to allocate a **limited budget** to food, lodging, and filling up the gas tank.
- There are several options for hotels and gas stations, from cheap to expensive and from distant to nearby.
- Risks – (a) Is a room in a hotel available? (b) Is cheap gas available at the nearest station?



Similarities between clinical trial monitoring and fuel consumption monitoring

Clinical trial		Fuel tank
QTL	↔	Tank capacity
Secondary Limit	↔	Fuel indicator level
Risk event	↔	Empty tank
Mitigation event	↔	The fuel indicator is on
Risk parameter	↔	% of full tank



Risk detected

A risk can be mitigated if resources are available

Methodology

Two interconnected mathematical models

Risk Optimizer

Selecting the optimal risk mitigation strategy

- Contingency budget allocation across risks
- Mitigation option selection for each risk
- Risk tolerance analysis

RBM simulator

Deriving efficient operational rules -

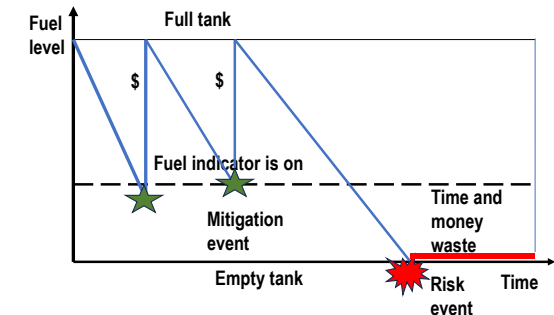
positioning of **QTL** and the **Secondary Limit thresholds** aligned with the risk assessment and contingency resources

Are all QTLs and Secondary Limits aligned with associated risks and the mitigation strategy?

Yes

No

Alignment of risk mitigation strategy and operational rules



Risk Optimizer

Therapeutic Innovation & Regulatory Science (2023) 57:717–727
<https://doi.org/10.1007/s43441-023-00521-5>

DIA

ORIGINAL RESEARCH



Efficient Risk Mitigation Planning for a Clinical Trial

Vladimir Shnaydman, Ph.D¹ 

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Risk Optimizer

- Each mitigated risk may have several mutually exclusive mitigation options. E.g., backup sites could be in country **X** or country **Y** or in both countries
- Each mitigation option is characterized by risk/probability (**R/P**), impact (**I**), risk score/average impact (**RxI**), mitigation costs (**M**), and risk-adjusted mitigation costs (**MxP**).
- Contingency budget - **B**

Risk and Risk Impact

Risk	1	2	3	4	5
Rating	Very low	Low	Medium	High	Very High
P – Av.%	10	25	50	75	90
P– range, %	5-15	15-35	35-65	65-85	85-95
Impact	1	2	3	4	5

Criteria:

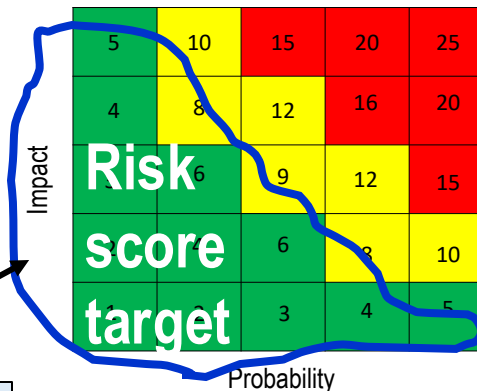
$$\text{Total normalized risk score (TNRS)} = \frac{\sum_i^N (R_i \times I_i)}{N} \quad \text{- Number of risks}$$

The optimization model – mixed linear integer programming model

Criteria – TNRS → min. **TNRS** for a trial should be in the “green zone” after the selection of a mitigation strategy

Constraints – contingency budget and mandatory mitigation of each significant risk.

Variables – X=(0,1) – selection of mitigation options



The model outcome

1. Efficient Contingency budget
2. An optimal risk mitigation option for each risk
3. Contingency budget allocation across risks

Example data

Modeling results

Input data

Output

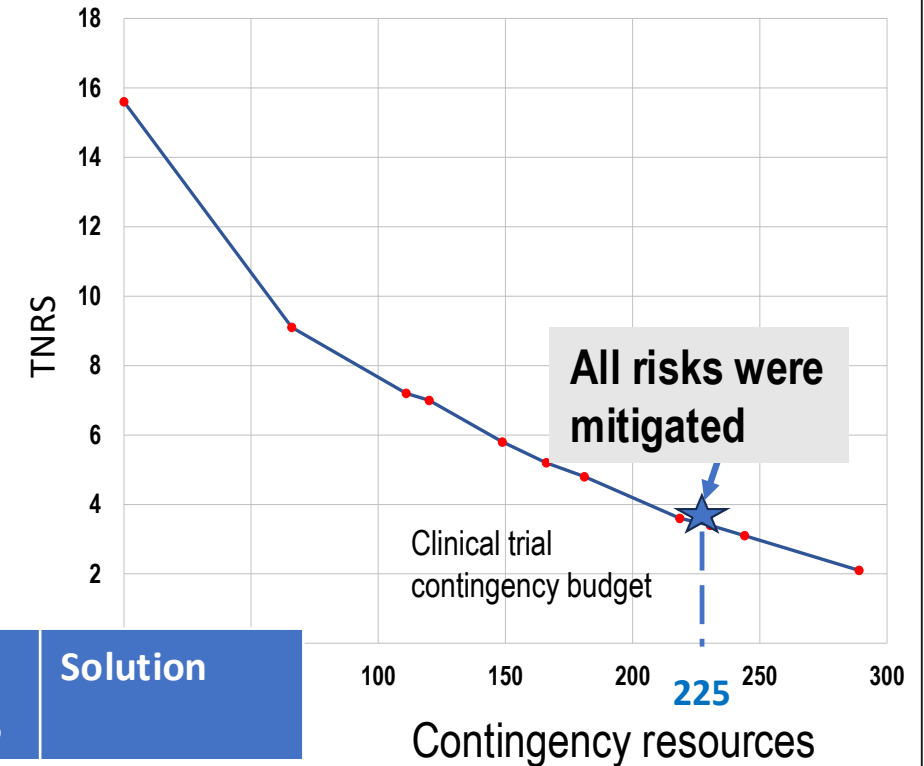
Mutually exclusive risk mitigation options

# Risk	Risk_Qual	Impact	Score	MITIG\$	Risk_Quan	ADJ MITIG\$	Solution
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

Mitigation option selected

$Risk_{AV} = 0.25$
Risk (range) $\rightarrow$ (0.15-0.35)

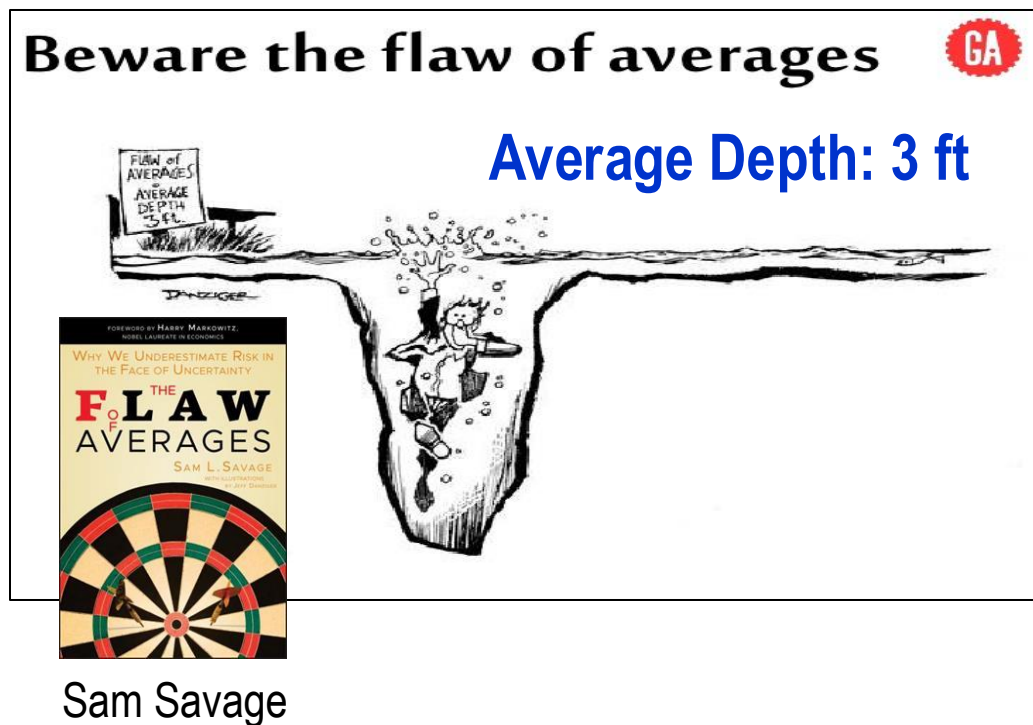
Total Normalized Risk Score (TNRS) vs. contingency budget



#Risk	Risk - Qualitative	Impact	Score (Rxl)	Mitig costs, \$	Risk-Quantitative	Risk adjusted Mitig. Costs, \$	Solution
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	1	12	0

Contingency planning and risk tolerance

The optimal risk mitigation model uses averages, e.g., risk mitigation costs and contingency budget.
“Average” contingency budget corresponds with a 50% chance that the mitigation strategy will be properly executed.



Risk tolerance

The level of risk an entity is willing to assume to achieve a potential desired result.

Risk tolerance =
 $= 1 - \text{Probability}\{\text{Contingency Budget will mitigate all risks}\}$



Risk capacity



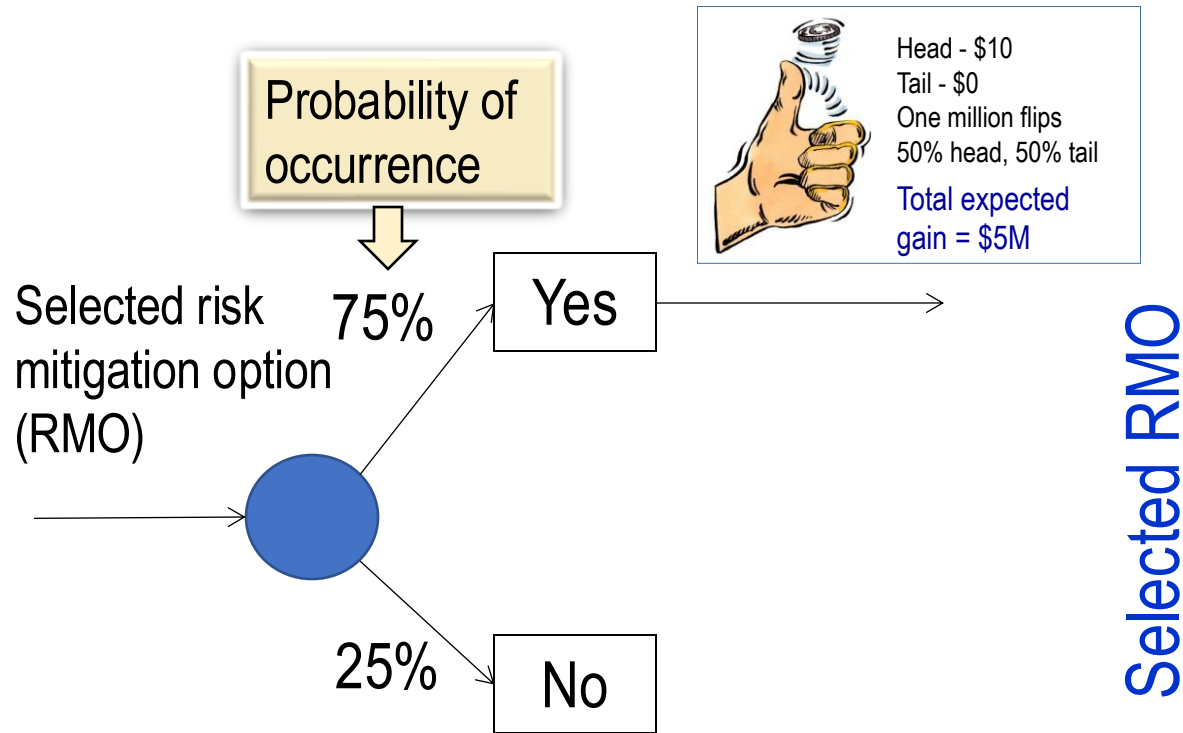
Risk appetite



Risk tolerance

Example: A company has a low-risk tolerance policy, i.e., it has substantial resources to mitigate all significant risks.

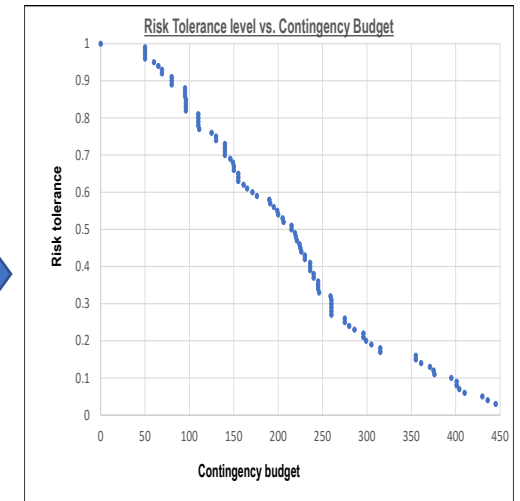
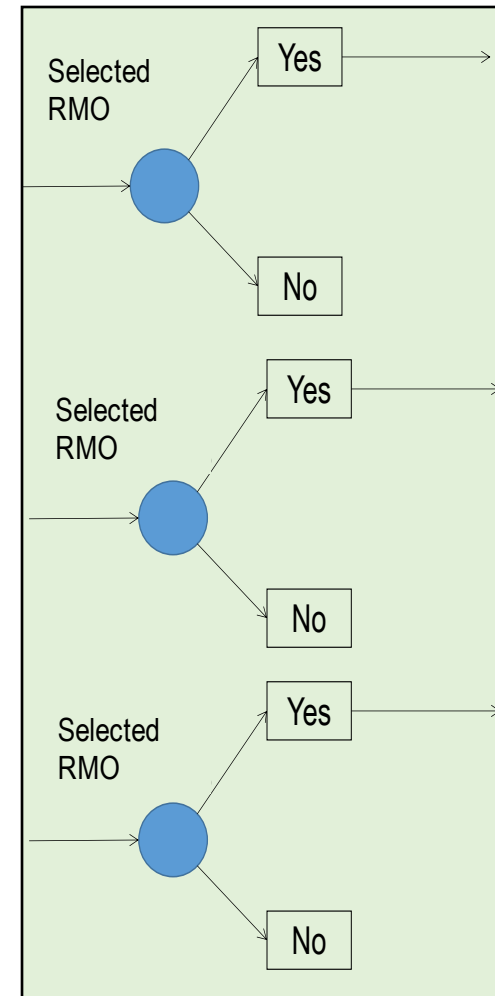
How to incorporate risk tolerance into contingency planning?

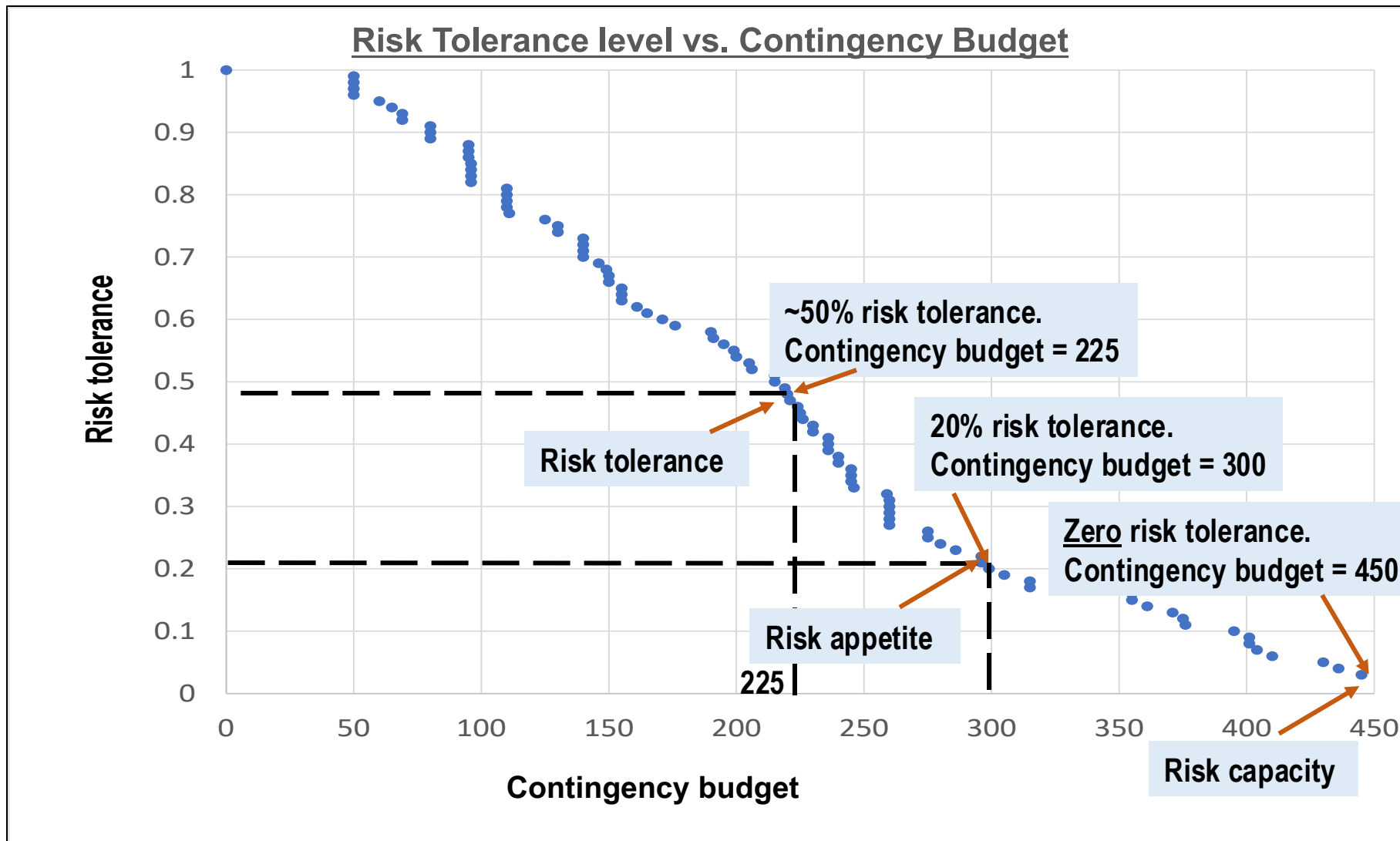


Risk

Score	5	4	3	2	1
Rating	Virtually certain	Likely	Even odds	Unlikely	Remote
Event Probability	90%	75%	50%	25%	10%

Monte-Carlo simulation of selected risk mitigation strategy (baseline scenario)





**Risk
capacity**



**Risk
appetite**



**Risk
tolerance**



- Zero risk tolerance requires a contingency budget~450 to minimize all selected risks
- Calculations based on average data are associated with a 50% level of risk tolerance
- For large companies with significant resources, the risk tolerance level is usually lower
- For smaller companies with limited resources, the risk tolerance level is higher

Risk tolerance level = 1- Probability{Contingency Budget will mitigate all risks}

Example: For contingency budget = 300, there is a 20% chance that risk mitigation strategy may not be accomplished

Summary – efficient risk mitigation strategy

- A contingency budget was derived to mitigate essential risks and aligned with risk tolerance.
- A contingency budget across risks was optimally allocated.
- A contingency budget aligned with risk tolerance.

- **How to validate the effectiveness of the developed mitigation strategy?**
- **How to develop efficient operational rules?**

RBM simulator

Therapeutic Innovation & Regulatory Science
<https://doi.org/10.1007/s43441-024-00722-6>

DIA

RESEARCH



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

Vladimir Shnaydman, Ph.D.¹

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RBM simulator

The RBM simulator mimics Risk Parameter dynamics for each risk

Input data

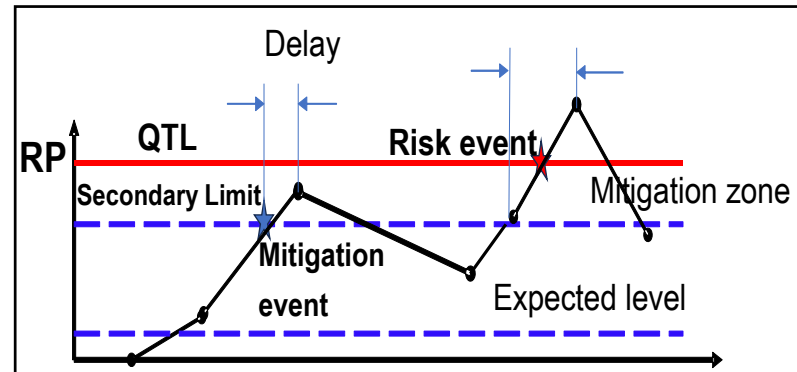
- QTL (**range**) or fixed
- Secondary Limit (SL) (range)
- Risk assessment
- Risk parameter deviation (min, max)
- Risk Parameter reduction due to the mitigation (min, max)
- Cycle time to resolve the mitigation of a risk signal (delay)
- Cost per mitigation action (min, max)

The model

- $RP(t+1) = F(RP(t))$
- Other conditions

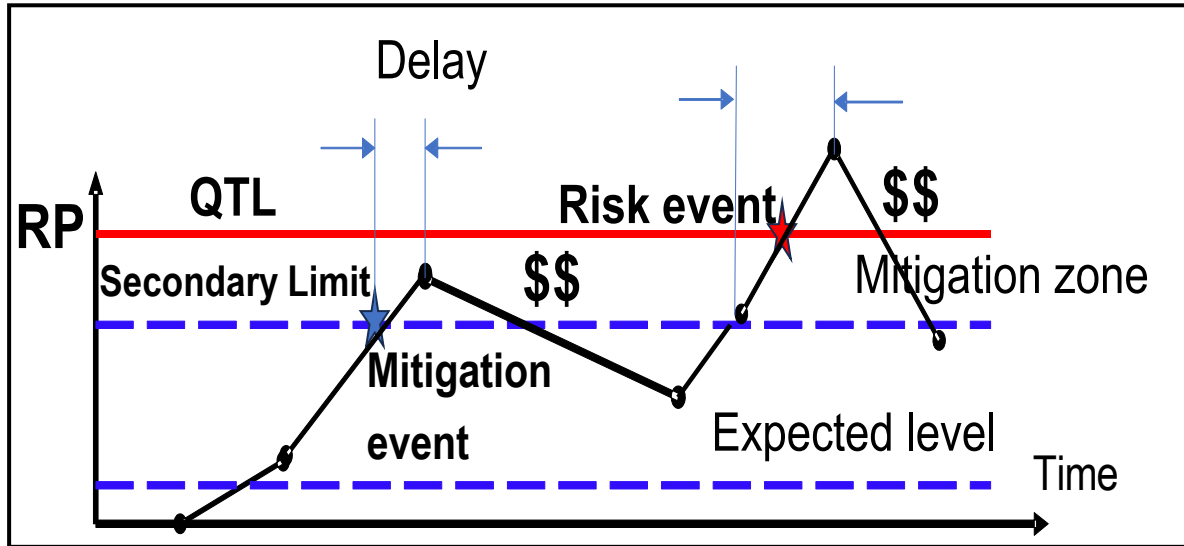
Output data

- The efficient QTL position
- The efficient Secondary Limit position
- Quantitative risk assessment
- Mitigation costs assessment



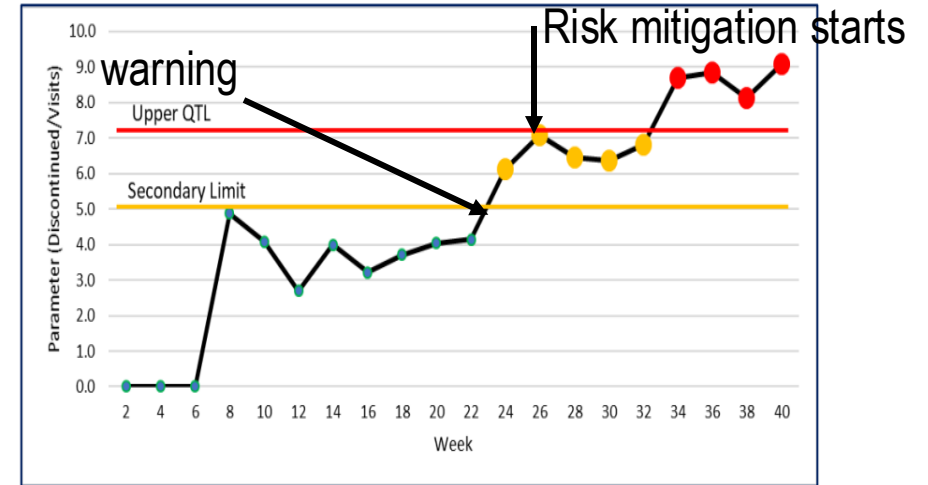
Two risk mitigation approaches

Proactive mitigation



The mitigation starts with a delay when an RP reaches or exceeds the Secondary Limit.

Reactive mitigation



Ensuring KRIs and QTLs Actually Work!

DRIVING QUALITY INTO CLINICAL TRIALS

Steve Young
Chief Operations Officer
CluePoints

Which approach is better?

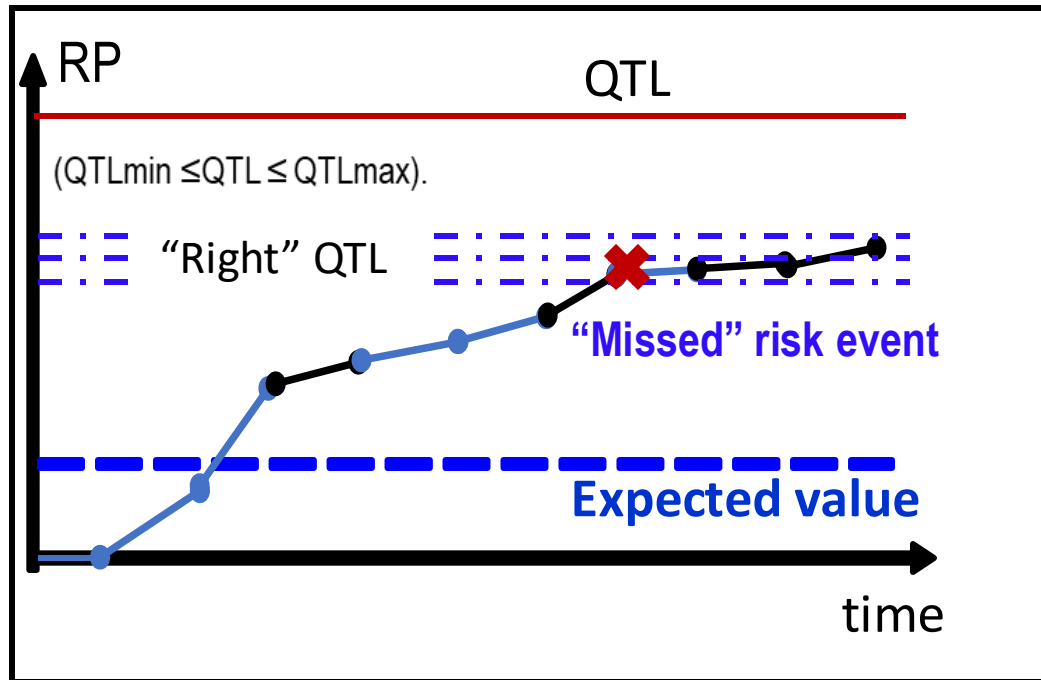
Analysis



1. QTL positioning

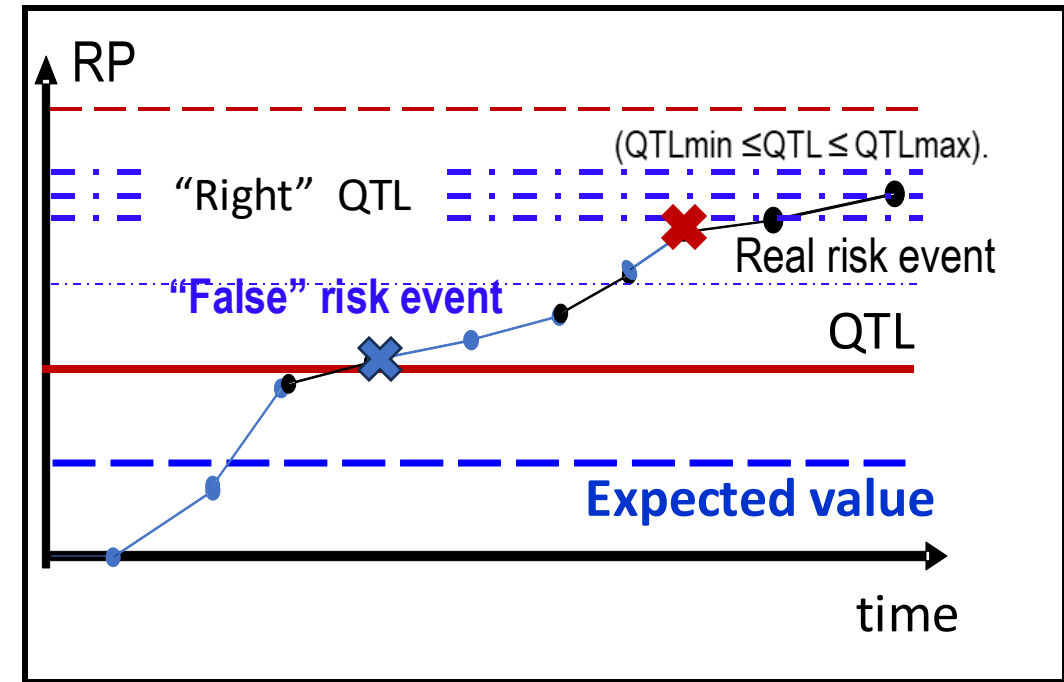
Current approaches – historical data, benchmarking, adjustment during a trial execution

QTL is too high



Missed risk event

QTL is too low



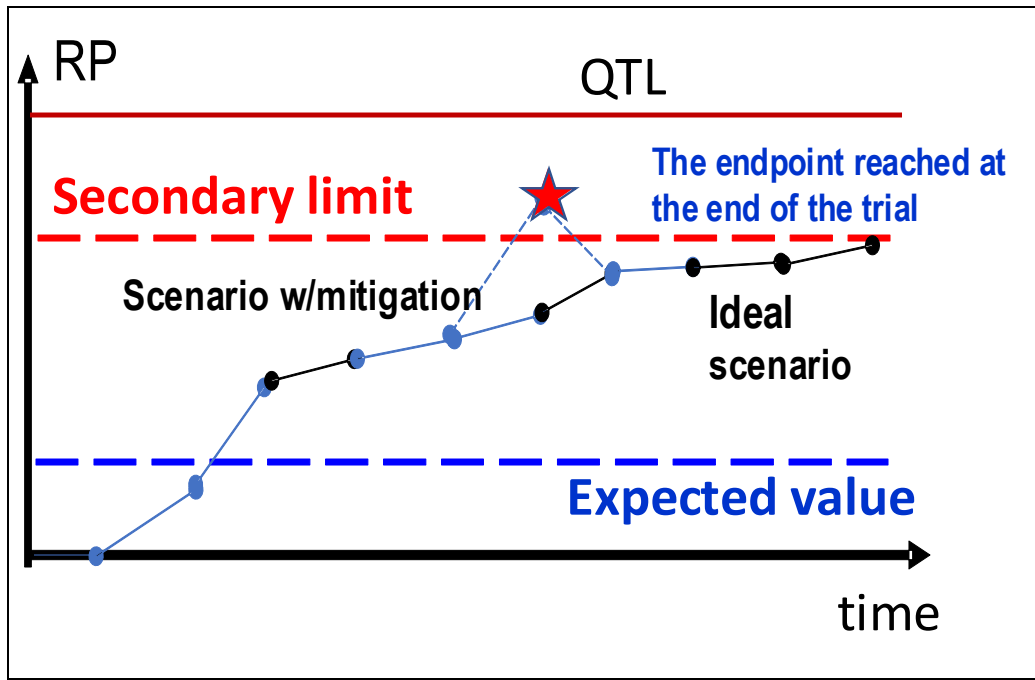
“False positive” risk event

How to position the QTL threshold efficiently?

2. Secondary Limit positioning

The current approach – Secondary limit could be set empirically, **e.g., 75% of QTL level**, or by statistical considerations based on historical data*.

Disadvantages: (1) Each trial is unique; (2) not many similar trials; (3) No alignment with risk assessment; (4) Validation only after a trial completion



How to position the secondary limit for each risk?

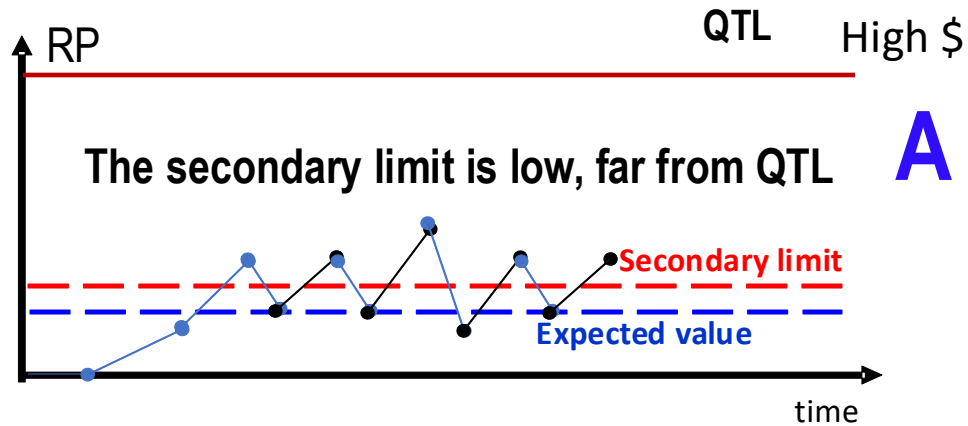
* Defining Quality Tolerance Limits and Key Risk Indicators that Detect Risks in a Timely Manner: Reflections from Early Adopters on Emerging Best Practices (Part 3)

April 12, 2022
WCG Metrics Champion Consortium QTL Working Group
Publication Article
Applied Clinical Trials
Applied Clinical Trials-09-01-2022
Volume 31 Issue 9

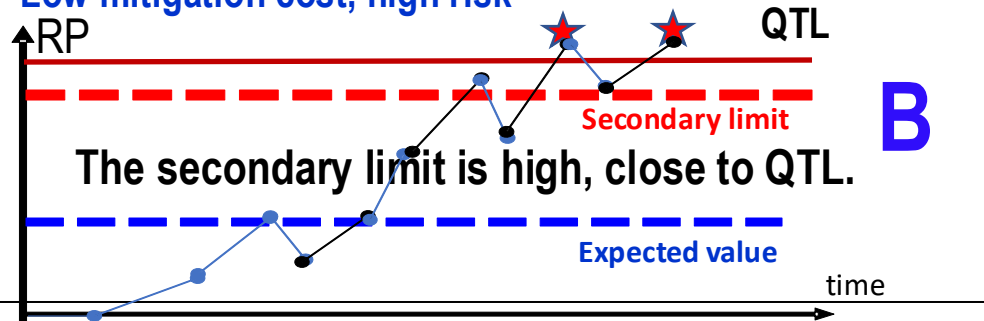
Two extreme cases of the Secondary Limit positioning

Proactive risk mitigation

High mitigation cost, low risk



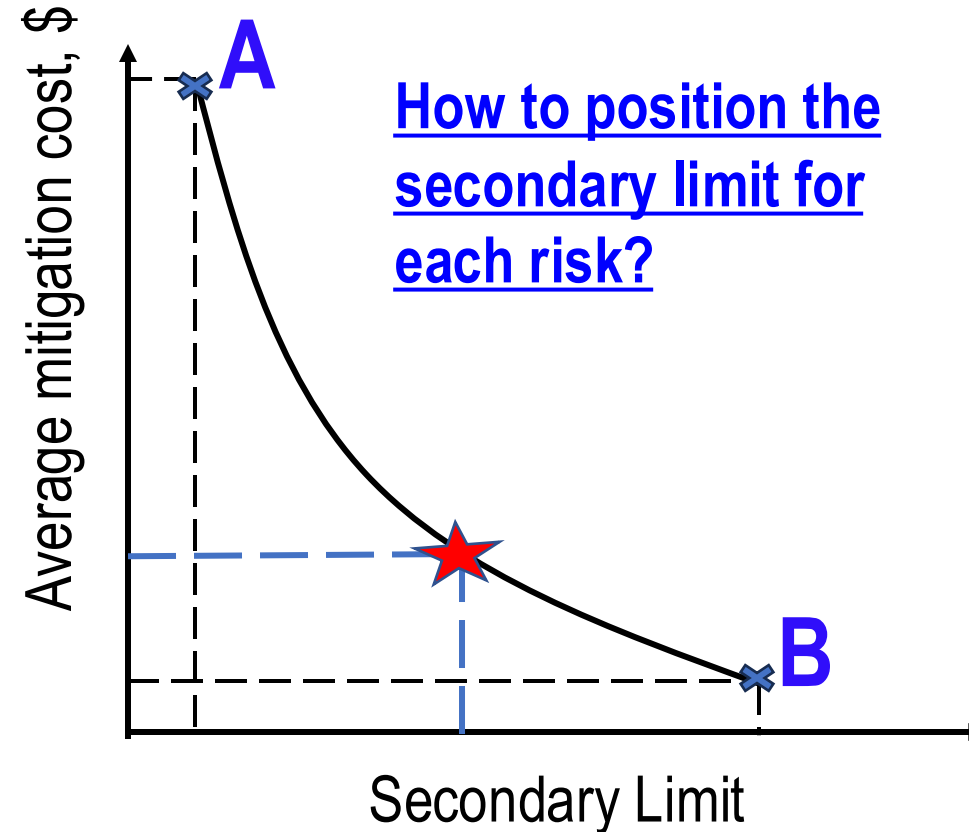
Low mitigation cost, high risk



QTL ↔ Risk assessment

Secondary Limit ↔ Contingency resources

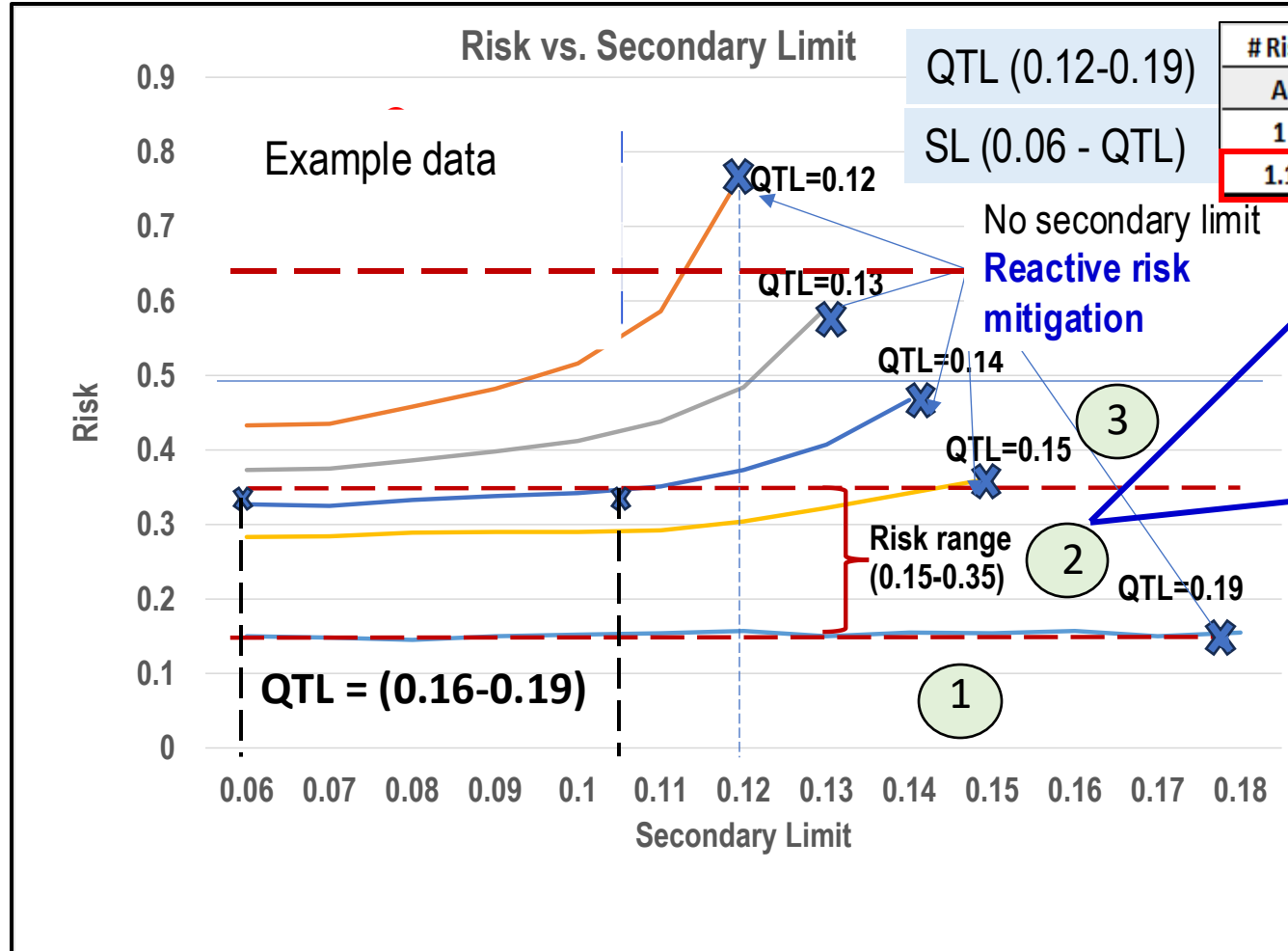
Each mitigation action needs resources.



Positioning of both thresholds should be coordinated

Modeling results

1. Deriving efficient QTL



The mitigation option selected for risk #1

# Risk	PROB_QUAL	IMPACT	Score	MITIG,\$	PROB_QUAN	ADJ MITIG,\$
A	B	C	D	E	F	G
1	3	4	12	0	0.5	0
1.1	2	4	8	15	0.25	3.75

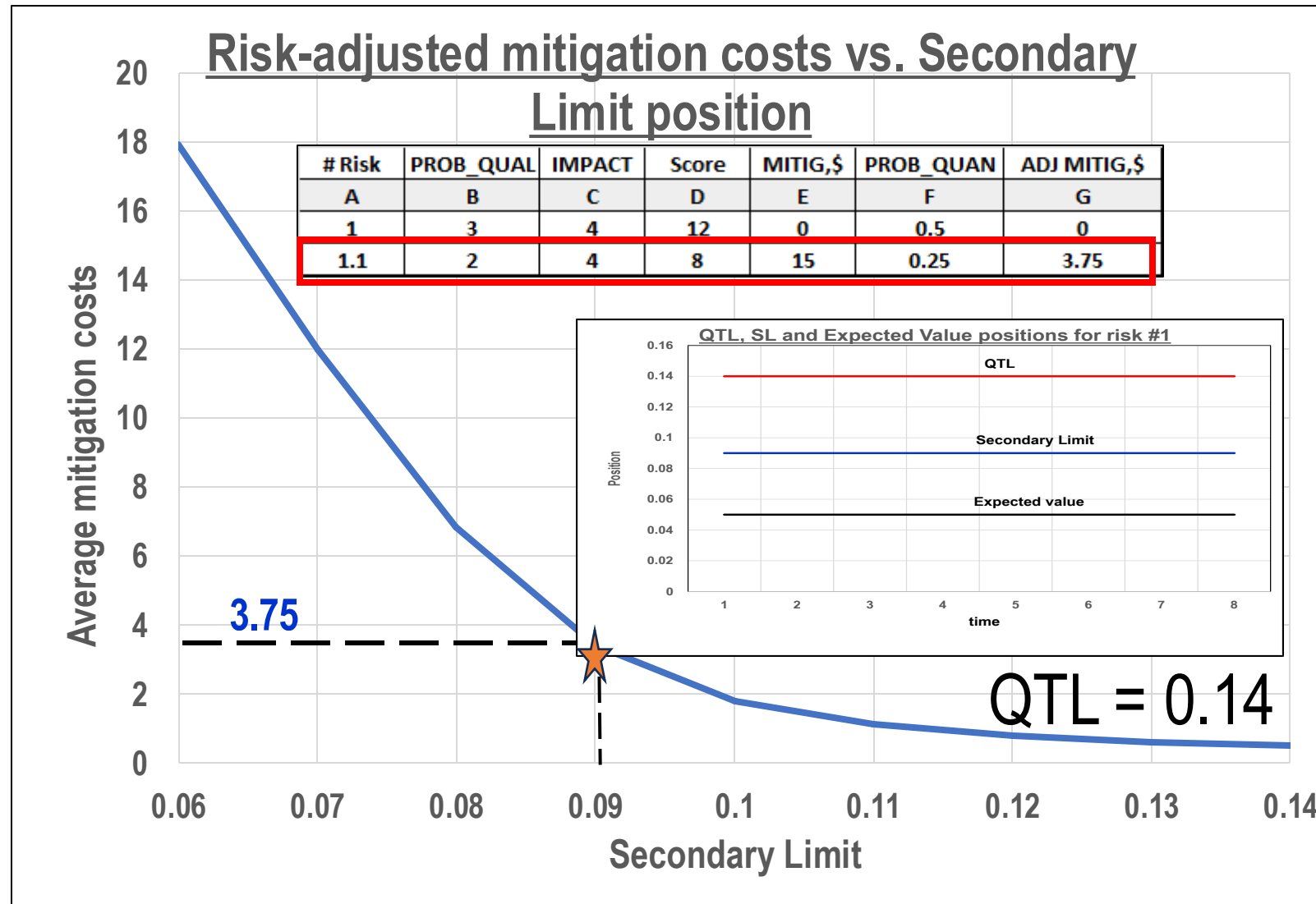
Risk	1	2	3	4	5
Rating	Very low	Low	Medium	High	Very High
Average, %	10	25	50	75	90
Range, %	5-15	15-35	35-65	65-85	85-95
Impact	1	2	3	4	5

Risk is the probability that a Risk Parameter will reach QTL.

Secondary Limit =(0.06-0.105) for QTL= 0.14

The risk is higher without the Secondary Limit

Secondary Limit positioning

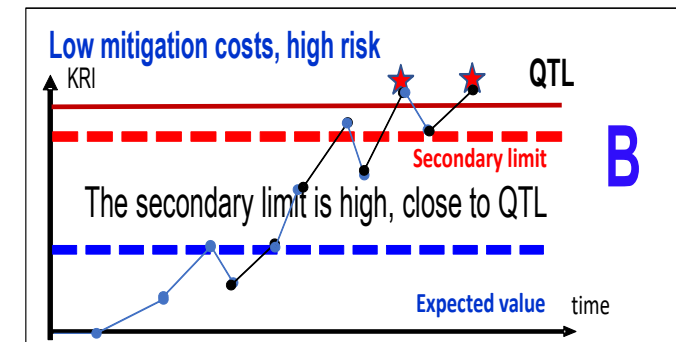
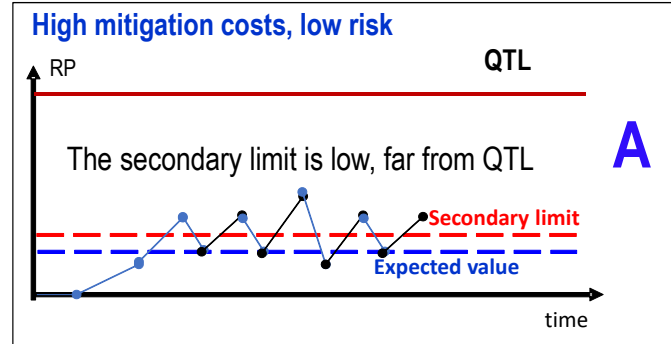


Secondary Limit =(0.06-0.105) for QTL= 0.14

Outcome:

QTL = 0.14

Secondary Limit = 0.09



Response to a risk signal in clinical trials

Industry Trends: Cycle Time to Resolve Risk Signals

June 6, 2023

Steve Young

Sylviane de Viron

Publication Article

Applied Clinical Trials

Applied Clinical Trials-06-01-2023

Volume 32 Issue 6

Processing and Closing Risk Signals

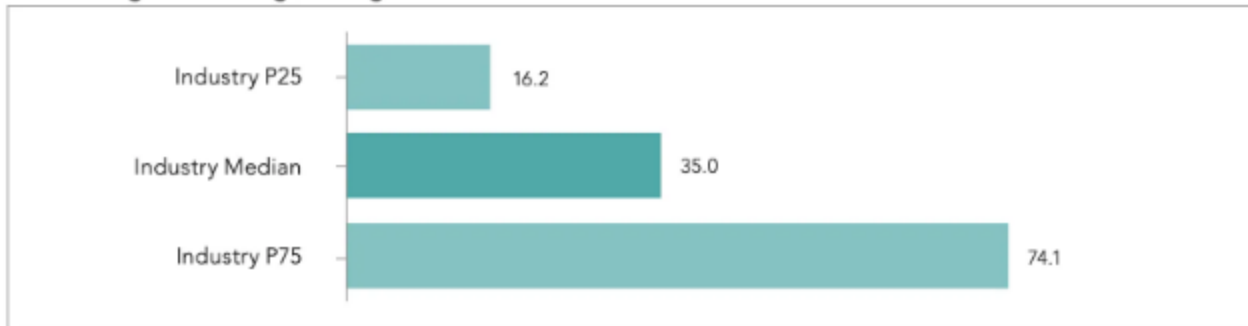


FIGURE 1. Industry trends for time to risk signal resolution (in days).

SOURCE: CluePoints

- Is the average cycle time acceptable?
- Could it be shorter?

Average cycle time for risk resolution = 35 days (16 – 74 days)

Risk mitigation in car racing – tire replacement (performance and safety)



Risk – blow-out tire

Risk mitigation – tire replacement

Risk mitigation efficiency components

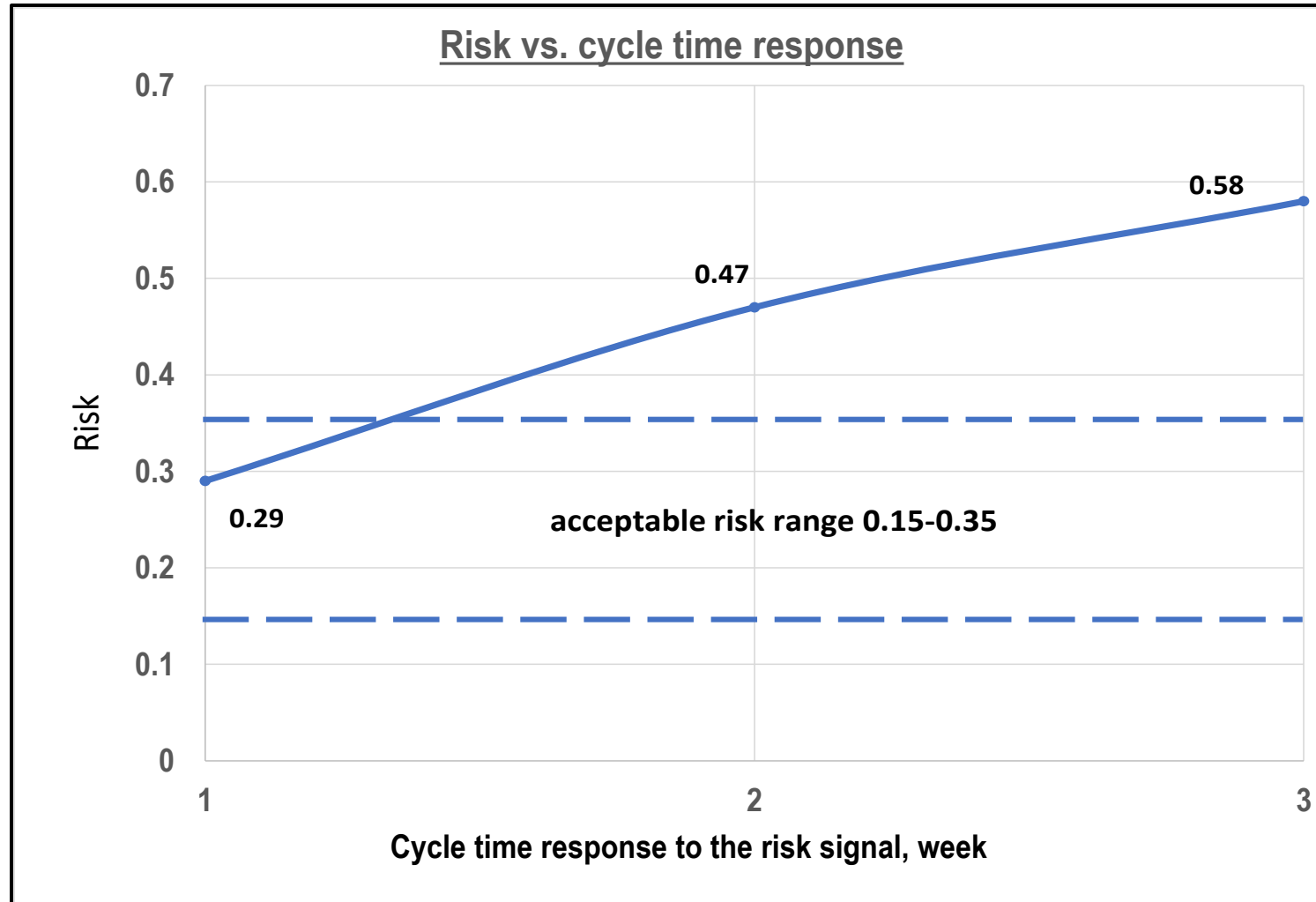
- Technology
- Resources efficiency (tires, equipment, and trained mechanics)
- Efficient processes and rules
- Cycle time

Four tire replacements ~ 20+ people

- **2023: less than two (!) seconds (1.8 sec)**
- 1950s: 67 seconds

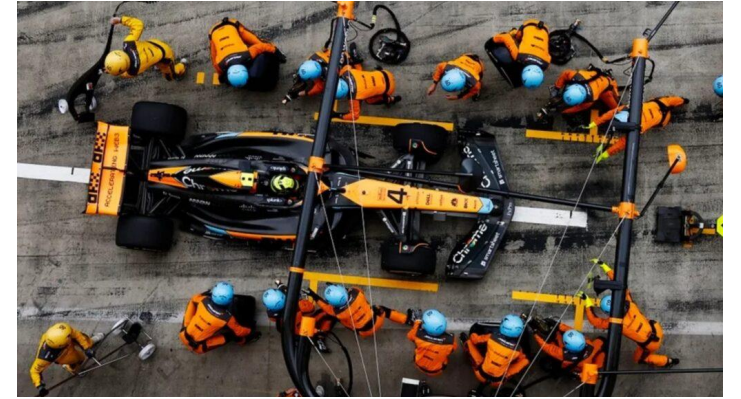
[Intense F1 Pit Stop Training \(youtube.com\)](https://www.youtube.com/watch?v=...)

Risk vs. cycle time response



Risk	1	2	3	4	5
Rating	Very low	Low	Medium	High	Very High
Average, %	10	25	50	75	90
Range, %	5-15	15-35	35-65	65-85	85-95
Impact	1	2	3	4	5

Key points



- Optimal allocation of the contingency budget across risks
- Efficient positioning of QTL and the Secondary Limit for each risk aligned with risk assessment and contingency resources allocation)
- Incorporation of the Secondary Limit reduces risk
- The technique could apply to large, medium, and small companies, and large, medium, and small clinical trials

Thank you!

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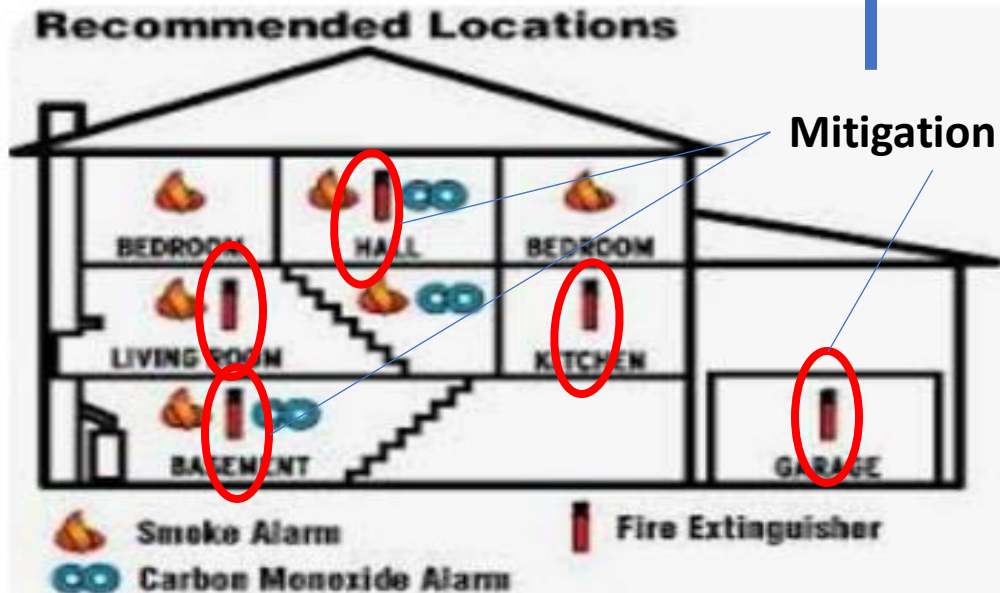
Do we need detectability?

$$I_{av} = I \times P + (1-P) \times 0$$

???

Risk Number = $\underbrace{(\text{IMPACT} * \text{likelihood})}_{\text{Average impact}} * \text{detectability}$

option #	Alarm (CO) x\$20	Alarm (smoke)x\$20	Fire Ext x \$30	Total cost, \$	Impact	Likelihood	Detectability	Risk number
1	0	0	0	0	3	1	3	9
2	1	0	0	20	3	1	3	9
3	2	1	1	70	3	1	2	6
4	2	2	1	110	3	1	2	6
5	2	2	2	140	2	1	2	4
6	3	3	3	210	1	1	1	1



Alarms (\$) + Fire Extinguisher (\$) = mitigation cost

- What if a house faces multiple risks (e.g., basement flooding, mold, leaking roof, etc.) under a limited contingency budget?
- How to allocate a contingency budget across multiple risks?
- How to position alarm thresholds in the absence of historical data?