

The background of the slide is a dark purple color with a complex, abstract network pattern. This pattern consists of numerous small, dark purple circles (nodes) connected by thin, light purple lines (edges), creating a web-like structure. In the top right corner, there is a solid, bright pink rectangular shape. The main title is written in white text, with the first part in a large serif font and the second part in a smaller, italicized serif font.

Quality Tolerance Limits: *Leveraging Predictive Modeling*

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Session Agenda

- Quality Tolerance Limits (QTL) Defined
- QTL Use in Manufacturing
- QTL Approaches in Clinical Trials
- PRA's Approach to QTLs
 - Application
 - Pros & Cons
 - Future Advancements
 - Lessons Learned

ICH-GCP E6(R2) Section 5.0

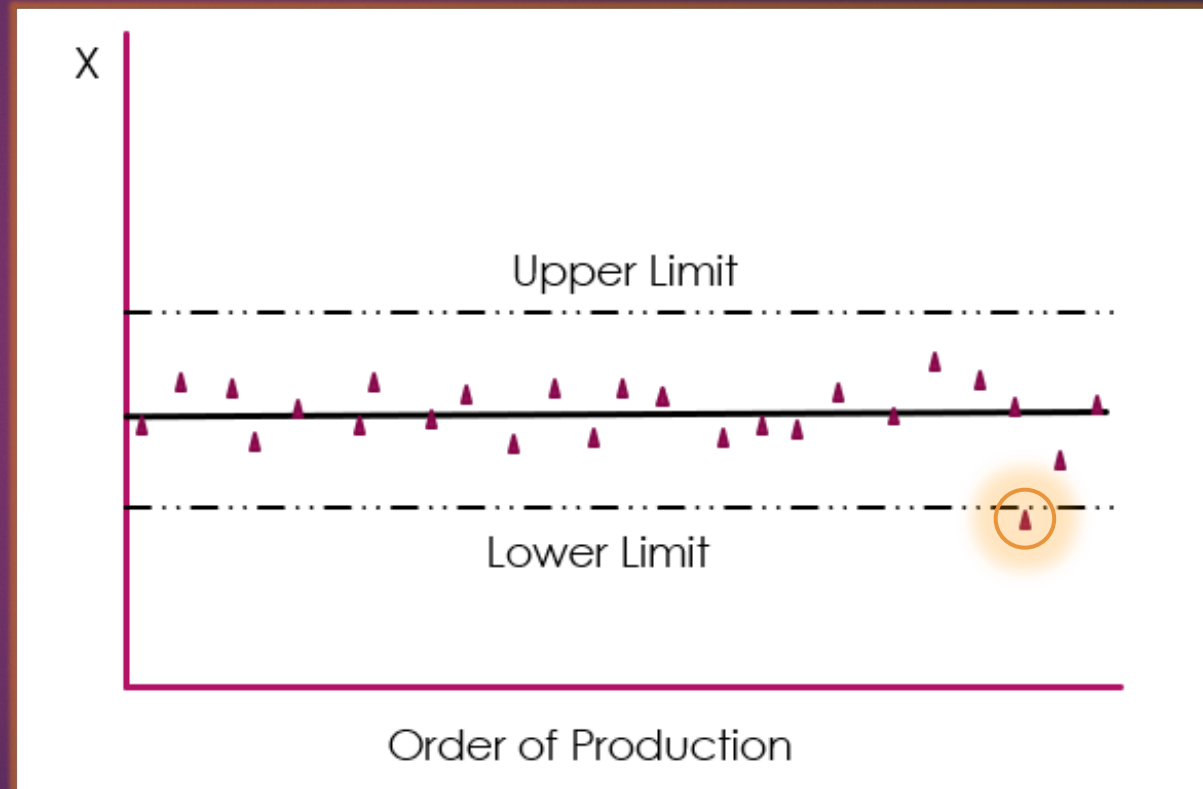
5.0.4 Risk Control:

- **Predefined Quality Tolerance Limits** should be established, taking into consideration the medical and statistical characteristics of the variables as well as the statistical design of the trial, **to identify systemic issues that can impact subject safety or reliability of trial results.**
- Detection of deviations from the predefined Quality Tolerance Limits should trigger an evaluation to determine if action is needed.

5.0.7 Risk Reporting:

- The sponsor should describe the quality management approach implemented in the trial and **summarize important deviations from the predefined Quality Tolerance Limits and remedial actions taken in the clinical study report** (ICH E3, section 9.6 Data Quality Assurance).

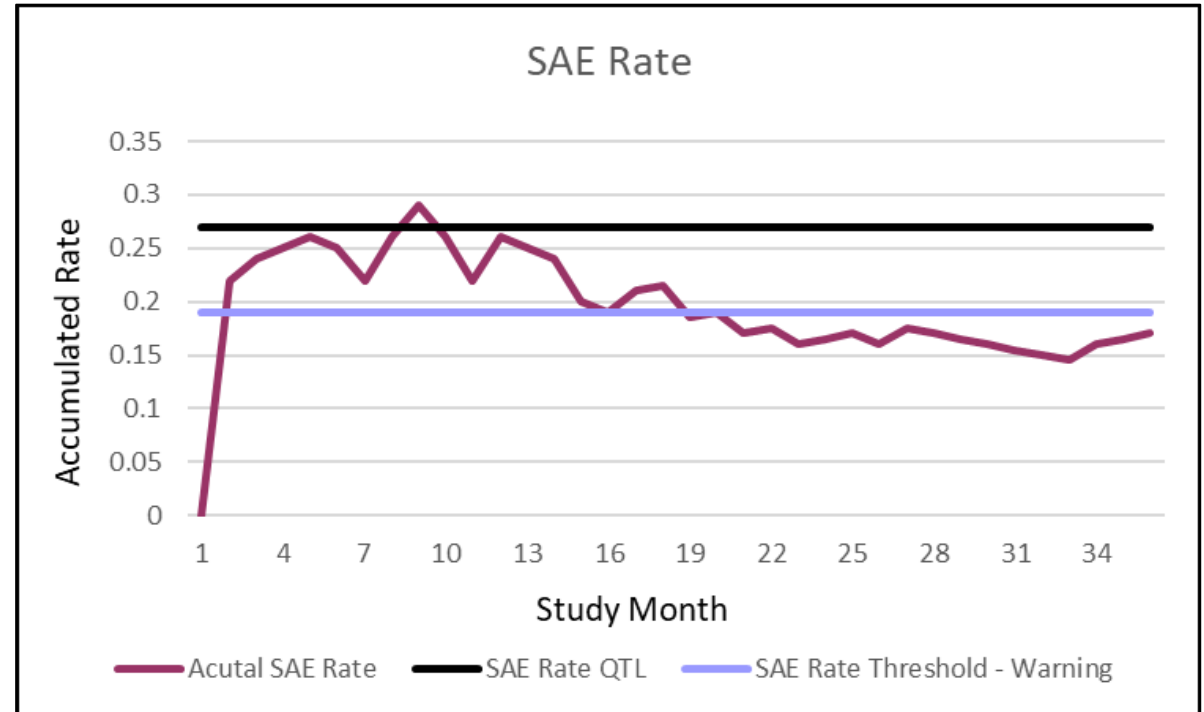
Manufacturing: Quality Control Charts



QTLs in Clinical Trials: Applied Approaches

Accumulated Rate

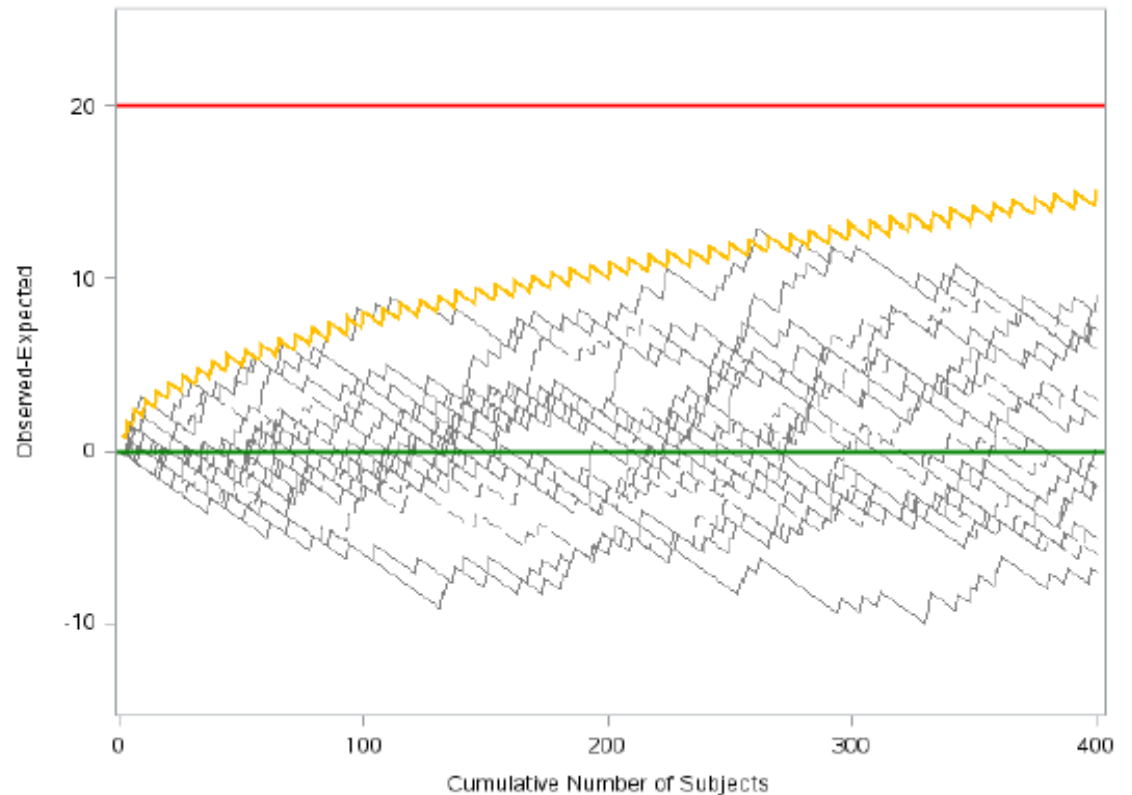
- + Most popular approach
- + Quicker/easier to set-up & apply
- + Well understood visualizations
- Strong propensity for non-systemic breaches (volatile)
- Unable to predict the future & overall study impact



QTLs in Clinical Trials: Applied Approaches

Statistical Process Control Charts

- + More sophisticated approach
- + Combination view of count & rate
- Complex to set-up & apply
- Not well understood visualization
- Often there is not enough data to accurately project/develop



PRA's Approach to QTLs

Purpose & Guiding Principles

- ▶ Create a library of QTL visualizations that:
 - ▶ Are applicable to the majority of clinical trials
 - ▶ Are efficient to set-up and well-understood by a project team
 - ▶ Pro-actively support the identification of trends & areas of concern
 - ▶ Reduce the likelihood of “false positive” QTL breaches
 - ▶ Predict the likelihood & timing of a “true” QTL breach during the trial

SAE Count

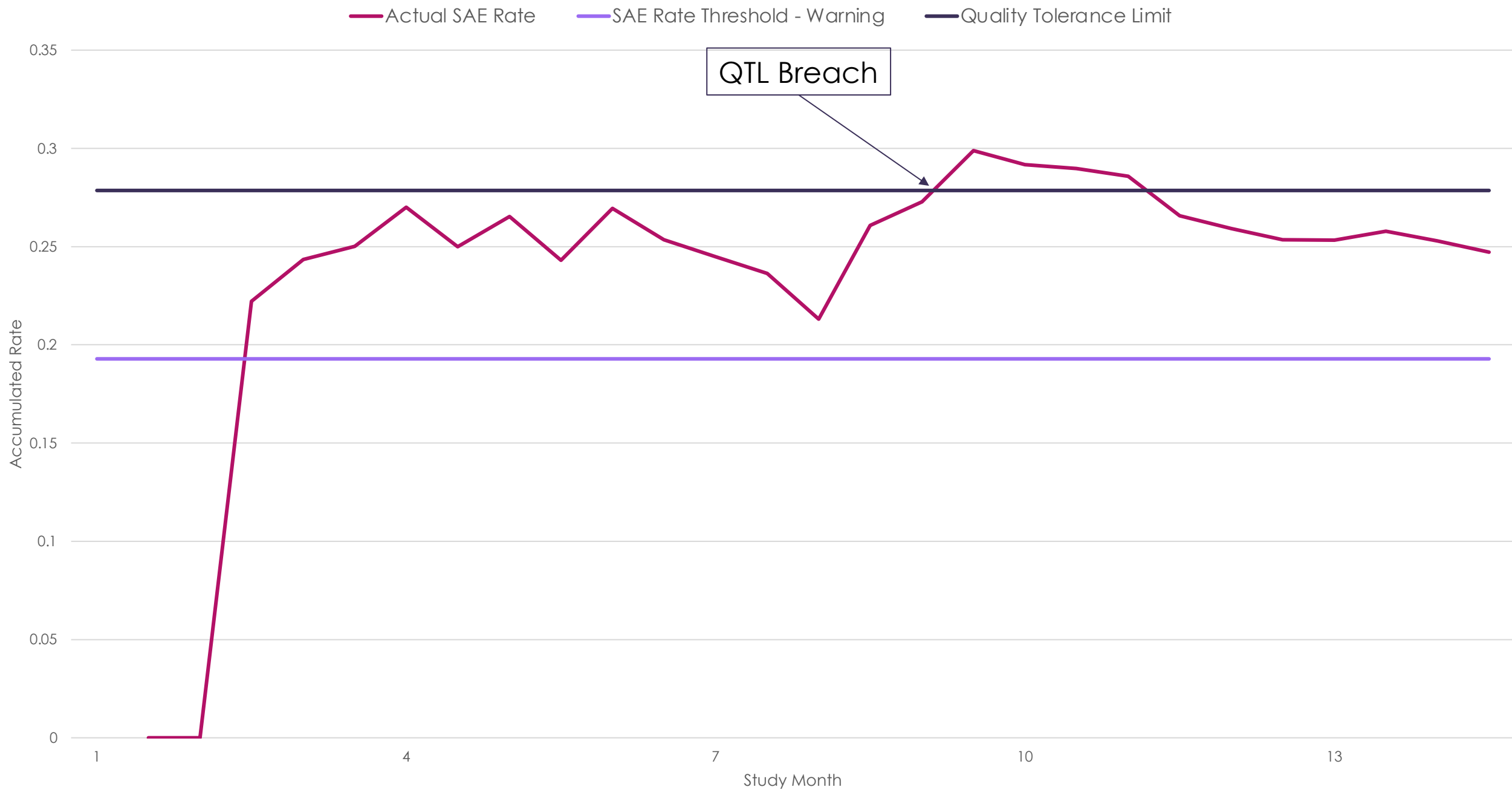
ET Count

IPD Count

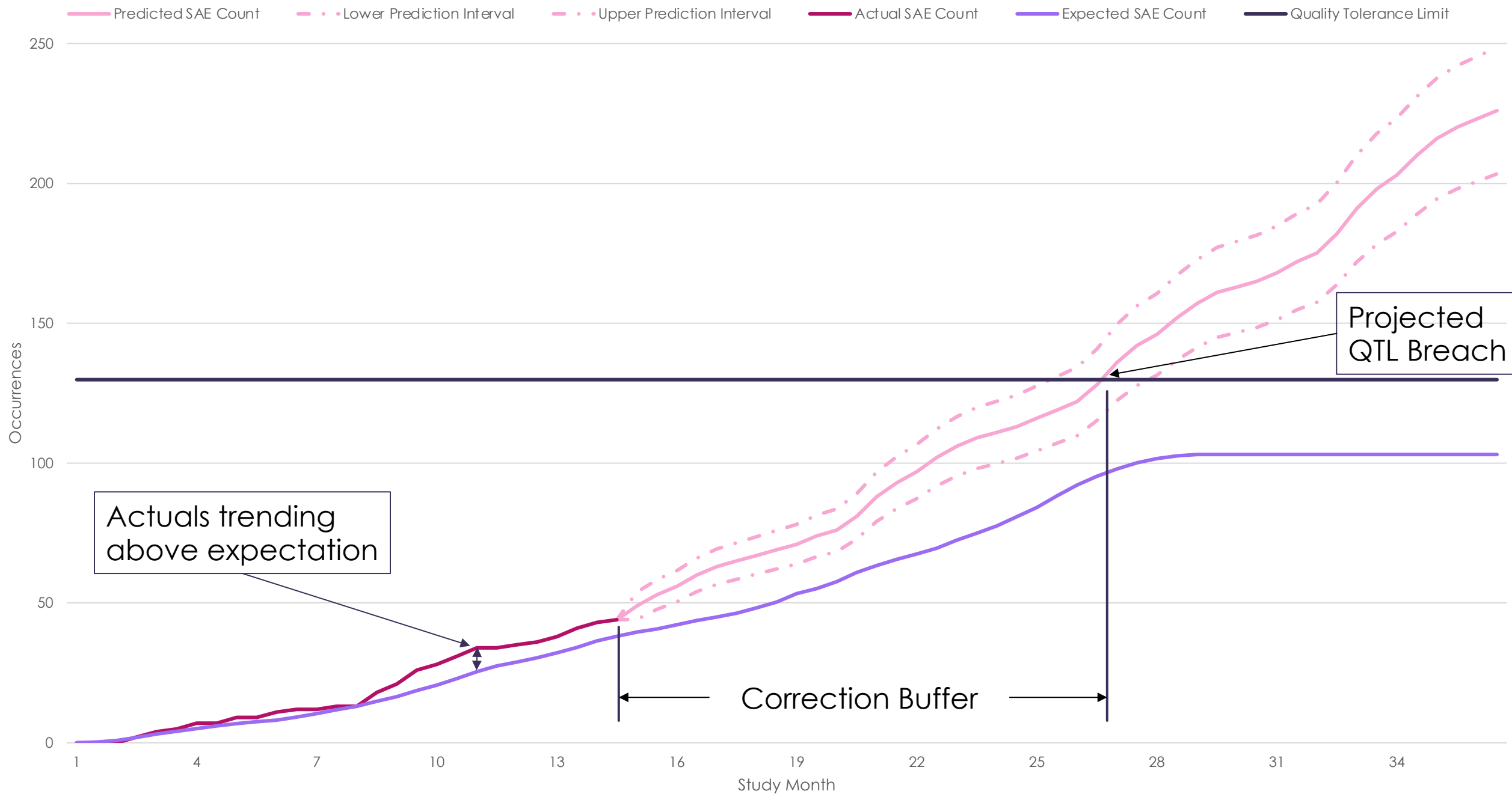
PRA's QTL Approach: A Two-Prong Review

- ▶ Develop a **QTL Count graph** & **Supplemental Rate graph** to be reviewed in a complimentary fashion
 - ▶ **SAE Rate Graph (supplemental)**
 - ▶ View month-to-month tracking of the cumulative SAE rate
 - ▶ Warning and alert threshold bands pro-actively identify SAE trends
 - ▶ **SAE Count Graph**
 - ▶ Monitors # of SAEs reported over the life of the trial
 - ▶ Incorporates the actual, expected, and predicted trend lines
 - ▶ Predicted trend line uses polynomial regression techniques along with seasonality
 - ▶ Expectation line uses subject months and expected SAE rate to represent how the study is tracking over time

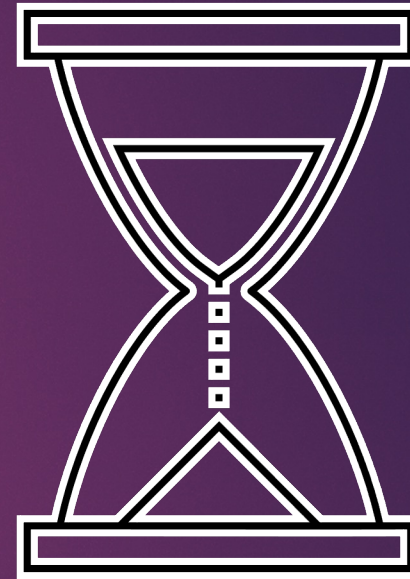
Traditional Rate-Based QTL



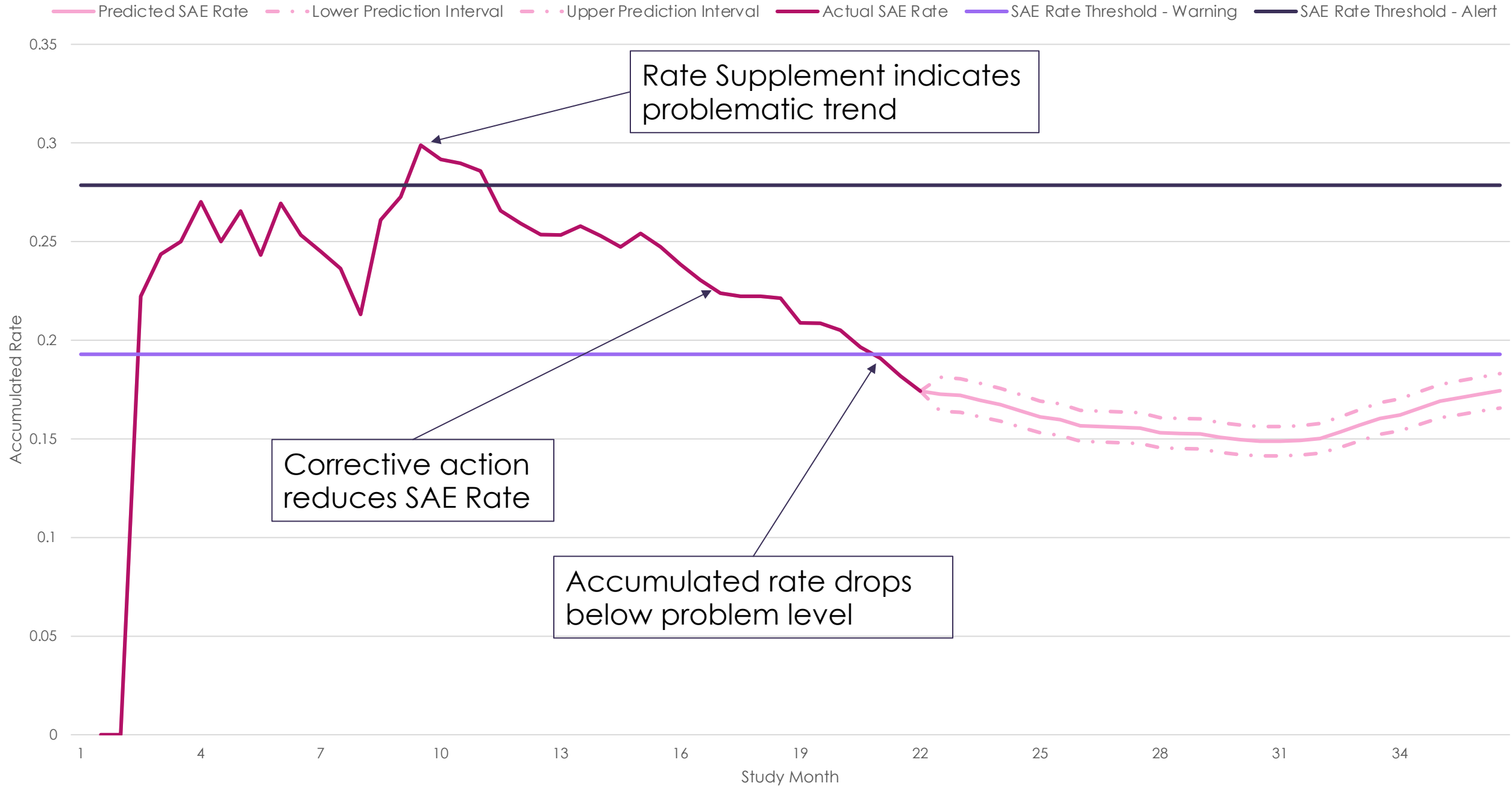
QTL Graph – Count



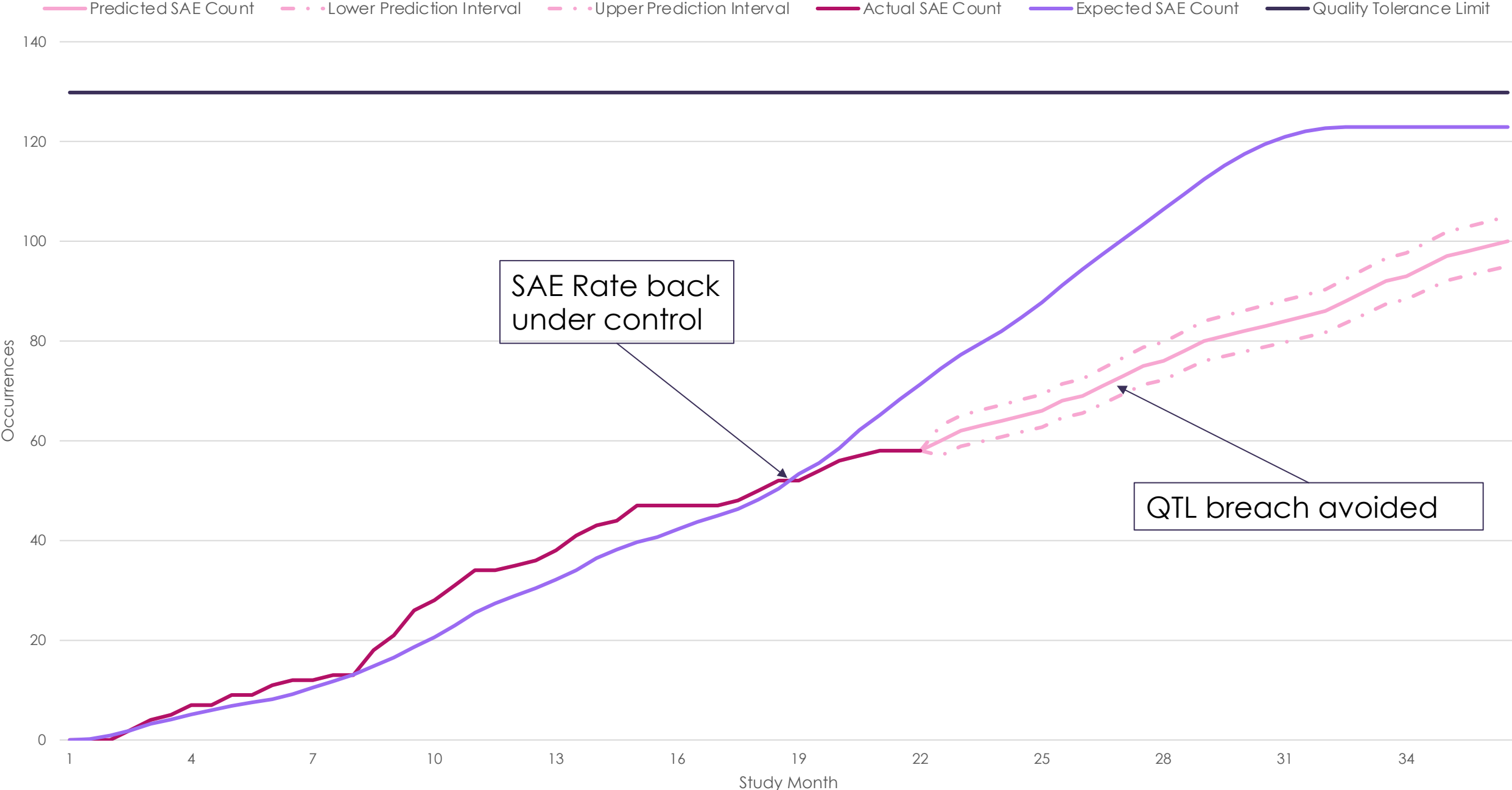
Fast Forward...



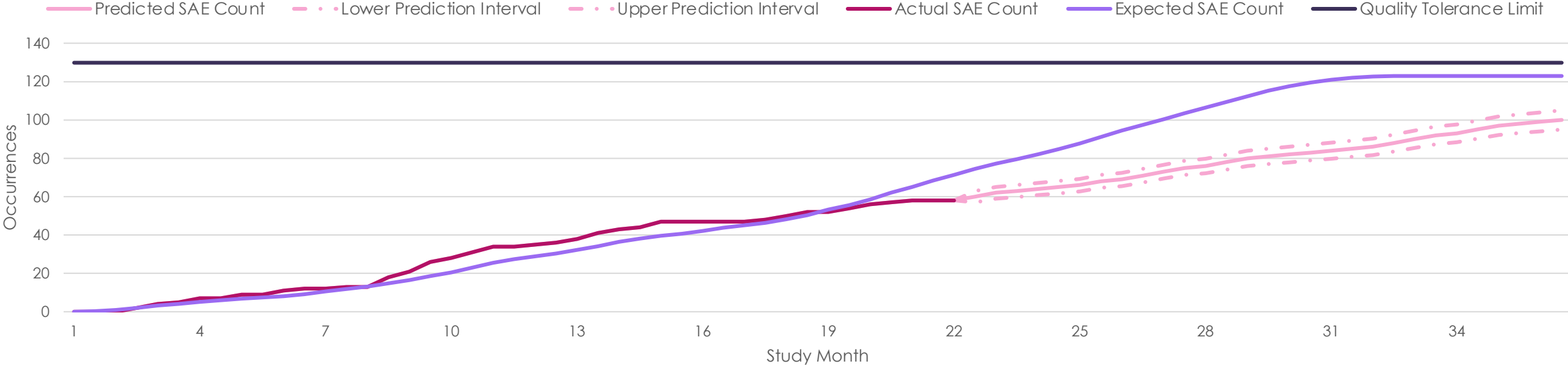
QTL Supplement – Rate



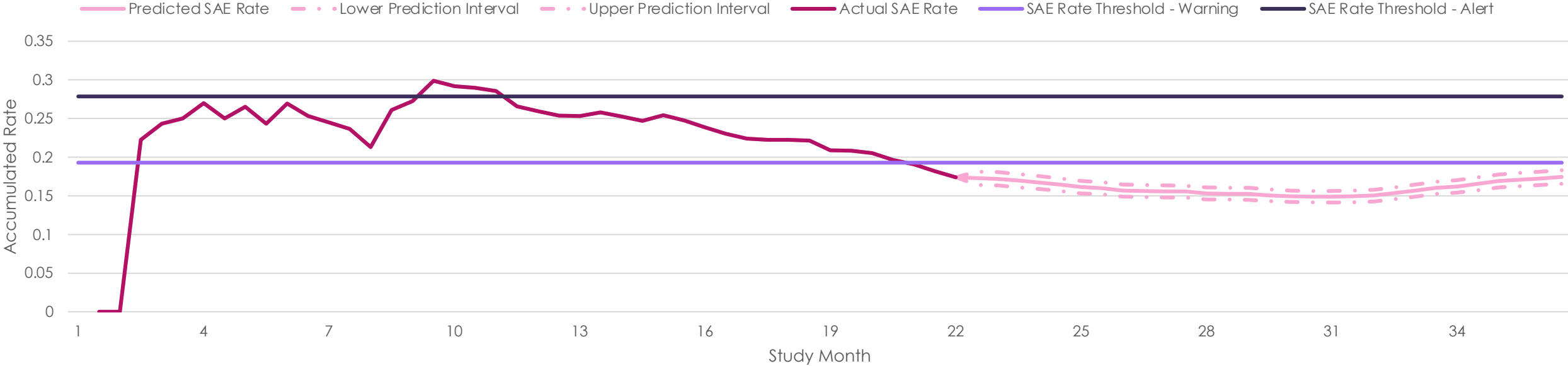
QTL Graph – Count



QTL Graph – Count



QTL Supplement – Rate



2-Prong Approach Pros and Cons

Advantages

- + Highly interpretable
- + Easy to set-up & apply
- + Early warning of future breaches
- + Reduced false positives
- + Conservative

Disadvantages

- Weaker statistical backing compared to SPC Charts
- Length of projections limited by input data
- Projection methodology needs refinement

Future Advancements

- ▶ Leverage cumulative data from studies of related ontologies to strengthen the confidence of QTL inputs
- ▶ Refine projection methodology
 - ▶ Multivariate Regression
 - ▶ Exponential Smoothing
 - ▶ ARIMA

Lessons Learned – Key Takeaways

- ▶ The Quality Tolerance Limits predefined at the beginning of the trial should be assessed routinely
 - ▶ Poorly hypothesized QTLs & Expected values (garbage in = garbage out)
 - ▶ Protocol amendments impacting QTL parameters (enrollment increases/eligibility criteria changes, etc.)
 - ▶ Any changes to QTL parameters should be summarized in the CSR
- ▶ Always keep the overall purpose of QTLs in the forefront
 - ▶ Monitor for systemic risks that impact subject safety and/or reliability of trial results

References

- ▶ Gilbert, SA., Pfizer. 2020. “Implementing Quality Tolerance Limits at a Large Pharmaceutical Company.” PharmaSUG 2020 – Paper SA-284
- ▶ Bhagat, R. 2020. “Quality Tolerance Limits: Framework for Successful Implementation in Clinical Development.” *Therapeutic Innovation & Regulatory Science*
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- ▶ TransCelerate . Risk-based quality management: quality tolerance limits and risk reporting.
<http://www.transceleratebiopharmainc.com/wp-content/uploads/2017/09/Risk-Based-Quality-Managment.pdf>. Published 2017. Accessed November 14, 2017.
- ▶ International Council for Harmonization. E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1): Guidance for Industry. <https://www.fda.gov/media/93884/download>. Published 2018.