**Selected Figures -- Assessing the Use of Quality Tolerance Limits in the Pharmaceutical Industry**

**PHUSE RBM Working Group – Quality Tolerance Limits Industry Survey 01Feb2022**

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**From:** Wells, Chris   
**Sent:** Friday, November 24, 2023 6:48 AM

Hi Steven

Thank you so much for the work you have completed. The new stacked bar charts look good and retain all the information we require. Just a couple of comments and if possible, request for some new plots. Could you review and advise how much work this would be and if this is too time consuming, i can work with Mike and Mireille to identify if we can remove any.

General point: for the plots that are stacked bar charts and where there are a number of different plots within the main plot (like plot 6) would it be possible to put the x axis at the top of the first plot as well as below the last plot? Just that it will enable the reviewer to follow the axis up and down easier.  Think this would apply to plots 6

Plot 3 - looks great.

A diagram of a number of different colored squares

Description automatically generated

Table - Plot 3: Othercategory breakdown

Total Count = 08

|  |  |
| --- | --- |
| Response Number | Other Functional Area |
| 1 | Clinical Trial Supplies, Contracts, and Imaging / Diagnostics |
| 2 |  |
| 3 |  |
| 4 |  |
| 5 |  |
| 6 | Central Monitoring, Imaging / Diagnostics, Risk Manager or RBQM lead, and SaaS programmers |
| 7 | Central Monitoring |
| 8 | Central Monitoring |
| 9 |  |
| 10 |  |
| 11 |  |
| 12 |  |
| 13 |  |
| 14 |  |
| 15 | Medical Monitoring, Medical Writing, and Project Management |

Plot 4 - this one equates to question 4 and is Which functional area Leads the trial level risk based approach to Quality.  - Could we have the same plot as you have created in plot 3.  this is very similar to plot 3 but plot 3 is asking which functional area is involved and plot 4 asks which function LEADS, so very slightly different

A graph with colorful squares

Description automatically generated

Table - Plot 4: Othercategory breakdown

Total Count = 08

|  |  |
| --- | --- |
| Response Number | Other Functional Area |
| 1 | Risk Manager |
| 2 |  |
| 3 |  |
| 4 |  |
| 5 | RBQM working group |
| 6 | Risk Manager |
| 7 | Central Monitoring |
| 8 | Central Monitoring |
| 9 |  |
| 10 | Oversight Team |
| 11 |  |
| 12 |  |
| 13 | Clinical Quality Management |
| 14 |  |
| 15 | Project Management |

Plot 5 - Question 5 - Trial types where company does not apply Risk Based Approaches to Quality   - could we have a plot like plot 3 by trial type (trial type on y-axis)

A diagram of a company

Description automatically generated

Table - Plot 5: Commentscategory breakdown

Total Count = 09

|  |  |
| --- | --- |
| Response Number | Comments |
| 1 |  |
| 2 | Studies with less sites or small sample size. |
| 3 |  |
| 4 |  |
| 5 | We try and offer something on Phase 1, Phase II, Phase III, and complex designs but its  not always possible. |
| 6 | Risk management to all studies but cetralized monitoring not for small sample size  studies or single site studies or with short duration studies - process under  implementation |
| 7 | RBQM concept driven by early/late clinical operations. |
| 8 | All studies are in scope. |
| 9 |  |
| 10 | All areas look at risk. |
| 11 |  |
| 12 | It’s been difficult to establish meaningful QTLS. |
| 13 | Observational and epidemiology study. |
| 14 |  |
| 15 | All studies considered to take risk-based approach as risk assessments and mitigation  planning are done for all. |

Plot 6 option 1 - Looks great but could we have the x axis at the top as well as the bottom.

Not great….

A chart of a diagram

Description automatically generated with medium confidence

Plot 6 option 2 - Looks great but could we have the x axis at the top as well as the bottom.

Better option.

A chart of data with different colored squares

Description automatically generated with medium confidence

Plot 7  - Could we have one for Question 7 like plot 3 but with the attributes on the y axis

A graph with numbers and a number

Description automatically generated with medium confidence

Plot 8 Option 1- Could we have one for question 8 like plot 6b and the attributes on the y axis and responses on the x-axis.

**Not great….**

A screenshot of a graph

Description automatically generated

Plot 8 Option 2 - Could we have one for question 8 like plot 6b and the attributes on the y axis and responses on the x-axis.

Better option.

A screenshot of a chart

Description automatically generated

Plot 10 - could we have a plot on question 10 - like plot 6 with attributes on y axis and response on x axis (top & bottom of the plot)

A chart of a company's risk-based approach to quality

Description automatically generated

Plot 18 - Question 18 - could we have a plot like plot 6b.02

A chart of data on a white background

Description automatically generated with medium confidence

Plot 19 - Question 19 - could we have a plot like plot 6b

A screenshot of a graph

Description automatically generated

Table - Plot 19: Commentsfree-text

Total Count = 04

|  |  |
| --- | --- |
| Response Number | Comments |
| 1 |  |
| 2 |  |
| 3 |  |
| 4 | Unknown at this time |
| 5 | We are still working on some of these areas. For secondary breaches, we may take  mitigating actions but would not report these in the CSR unless it lead to a protocol  amendment or something like this. For primary breaches, these would be discussed in  the CSR however sometimes the qtl setting using the historic data may not be applicable if the historic study was not a good match. So then this may result in the review of the  distribution and also may result in an amendment of the QTL thresholds. |
| 6 |  |
| 7 |  |
| 8 |  |
| 9 |  |
| 10 |  |
| 11 |  |
| 12 | Have not yet happened - the action would depend on kind of breach, severity etc. |
| 13 | None of these actions are planned in advance.  We try to mitigate the critical to quality  risks proactively, and then meet to assess on an ongoing basis.  There have been  instances where we needed to change the QTL because it was set incorrectly, although  that has not happened since we put the dedicated RBQM team in place to manage the  process. |
| 14 |  |
| 15 |  |

Plot 20.3 - question 20.3, could we have a plot like plot 3

A graph of a number of data

Description automatically generated with medium confidence

Table - Plot 20.3: Commentsfree-text

Total Count = 04

|  |  |
| --- | --- |
| Response Number | Other reasons |
| 1 |  |
| 2 |  |
| 3 |  |
| 4 |  |
| 5 | The guidance is given to document all primary breaches in the CSR. |
| 6 |  |
| 7 | No clear guidance, study by study and case by case decisions. |
| 8 | After assessing if it is a true breach by all roles. |
| 9 |  |
| 10 |  |
| 11 |  |
| 12 |  |
| 13 | We report all QTL breaches and discuss how it will be reported. |
| 14 |  |
| 15 |  |

Plot 23 – QTLs parameters defined by **TransCelerate**

A sheet of music with text

Description automatically generated

Table - Plot 23: Commentsfree-text

Total Count = 03

|  |  |
| --- | --- |
| Response Number | Other reasons |
| 1 |  |
| 2 |  |
| 3 |  |
| 4 |  |
| 5 | We have used a standard set of parameters, over/under reporting of rate of aes, over  reporting of rate of saes/protocol deviations and also proportion of patients with a  baseline deviation. However we are moving towards picking parameters to support the  estimand framework |
| 6 |  |
| 7 |  |
| 8 | Annual dropout rate, trial disposition |
| 9 |  |
| 10 |  |
| 11 |  |
| 12 |  |
| 13 | QTLs are very study specific, so others are always under consideration. |
| 14 |  |
| 15 |  |

## Plot 23 - rates

A chart of different colored squares

Description automatically generated

Plot 24 - question 24

A chart of numbers and text

Description automatically generated with medium confidence

Table - Plot 24: Commentsfree-text

Total Count = 03

|  |  |
| --- | --- |
| Response Number | Other reasons |
| 1 |  |
| 2 |  |
| 3 |  |
| 4 |  |
| 5 |  |
| 6 |  |
| 7 |  |
| 8 |  |
| 9 |  |
| 10 |  |
| 11 |  |
| 12 |  |
| 13 | Additional QTLs are always under consideration. |
| 14 |  |
| 15 |  |

## Plot 24 - rates

A screenshot of a graph

Description automatically generated