Paper AR01

Quality Tolerance Limits: Statistical and Programming Consideration

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ABSTRACT

Quality Tolerance Limits (QTLs) as part of overall ARBM strategy is gaining traction in the industry and Health Authority (HA) alike. Predefined QTLs, taking into consideration medical and statistical characteristics of the variables as well as trial design are the cornerstone of this process.

In the current QTL strategy at Janssen R&D, the QTL core team (Physician, Statistician, Clinical & Statistical Programmer, Trial Manager, Central Monitoring Manager) has the overall responsibility to define, monitor and report on the QTLs.

The Statistical Programming is involved at the Define stage by providing specific programming inputs. During the Monitoring stage they are providing additional data for the study teams when a breach occurs. They are heavily involved at the Reporting stage to create CSR outputs. This paper discusses programming and statistical considerations to make while defining QTL parameters and corresponding thresholds. Using a case study, it demonstrates how QTL can be implemented.

INTRODUCTION

As per ICH E6 (R2), Quality Tolerance Limit (QTL) was established to identify systematic issues that can impact subject safety or reliability of trial data and ensure that important deviations from predefined QTLs and associated remedial actions taken are documented in Clinical Study Report (CSR), and in doing so, modernise quality control of clinical trials. To do so, TransCelerate Biopharma developed a framework to guide trial sponsors and their associates for successful implementation of QTLs with maximum efficiency, safety of trial participants and reliability of trial data.

Historically, QTLs have been required for Good Manufacturing Practices (GMP) to ensure the manufactured product achieve desired quality. However, since 2016, QTL became a part of regulatory requirement for clinical trials as per Good Clinical Practices (GCP). There are different statistical approaches to define QTLs and their subsequent monitoring. Early engagement of medical and statistical expert with knowledge of similar trials, assessment of historical data from similar trials, simulation and modelling, known or anticipated risk factors of the trial are all come into the picture while making attempts not to compromise with the power of the study. The overarching principal of these approaches are guided by ICH E6 (R2) Section 5.0.4: “The Sponsor should decide which risks to reduce and/or which risks to accept. The approach used to reduce risk to an acceptable level should be proportionate to the significance of the risk…”.

There are 3 key stages in the QTL framework - Define, Monitor and Report. At the define stage, the statistician and medics are responsible for defining QTL parameters and corresponding threshold keeping unique necessities of the trial in mind. They need specific programming inputs like potential

availability and timing of availability of data, derivation methods for parameters, draft data presentation scheme etc. During the monitoring stage, the process needs regular monitoring and reporting, and any breach of threshold will warrant appropriate action. At this stage, additional details about the programmed output can be added in data presentation scheme in terms of required outputs to support reporting major QTL deviations in CSR. The last stage requires a summary report of QTL deviations and associated preventive and/or corrective actions (analysis outputs – tables, listings, graphs) at the end of the trial. The highlights or important QTL deviations and associated actions would be included in the clinical study report (CSR). Statistical Programmers have a major role to play at this stage.

SOME STATISTICAL PRINCIPLES GUIDING QTL

While defining QTL parameters, the study statistician needs to keep in mind some guiding principles such as - What is the primary objective of the study? What is the key question that the trial is trying to answer? What's the data analysis plan? What's the most critical to quality data? Does the study have iARBM plan in place? What are the Key Risk Indicators (KRIs) for the study?

In the define stage, the study statistician may want to revisit historical studies of similar objectives. In addition to that, the study statistician may also want to link the primary and/ or secondary objective with the QTL parameters. To determine the threshold, the statistician may want to simulate study data to analyse different scenarios to evaluate its impact on the power of the study. Historical data from similar studies will aid at this stage. Likewise, a secondary threshold for each parameter can be derived. The secondary threshold acts as an early warning, so the team can be alerted if additional mitigation can be deployed to avoid actual QTL breach.

QTL IMPLEMENTATION – A CASE STUDY FROM A PHASE 3 ONCOLOGY STUDY

The Trial: Randomized open label, multicentre phase 3 study evaluating subjects with newly diagnosed multiple myeloma.

Secondary Objectives: Key secondary objective:

- Progression-Free Survival (PFS)

Sample size: 360 patients –This is to achieve a power of 80% with alpha = 0.05. Actual N = 395.

Key secondary endpoint: PFS

This sample size gives approximately 80% power to detect 37% reduction in the risk of progression or death (HR=0.63; median PFS from 43 months to 68 months). Interim Analysis was planned at 98 PFS (60% of events). Final analysis was projected at 162 PFS events (or 205 events if observed HR at IA is >= 0.7)

QTL PARAMETER AND THRESHOLD

Critical to Quality	QTL Parameter	Justification	QTL primary threshold	Justification for primary threshold	QTL secondary threshold	Justification for secondary threshold
Disease Evaluation (DE) assessments must be done as per schedule	≥ 2 consecutives missed DE followed by PFS event (PD or death) *	Per FDA's feedback, subjects who miss 2 or more consecutive DEs should be censored at the last DE before missed DEs. This impacts the power of the study.	10% of subjects with ≥ 2 consecutive missed DE followed by PFS event. Total # of PFS events as denominator	Power estimates of various scenarios, and historic rates from previous Drug A trials	5% of subjects with ≥ 2 consecutive missed DE followed by PFS event. Total # of PFS events as denominator	To allow enough time to prevent to reach primary threshold and implement corrective action plan.

**QTL core team eventually set upon the QTL parameter based on secondary endpoint since the primary MRD analysis was already completed at the time of official QTL implementation.*

PROGRAMMING INPUT: A DEDICATED ADAM DATASET

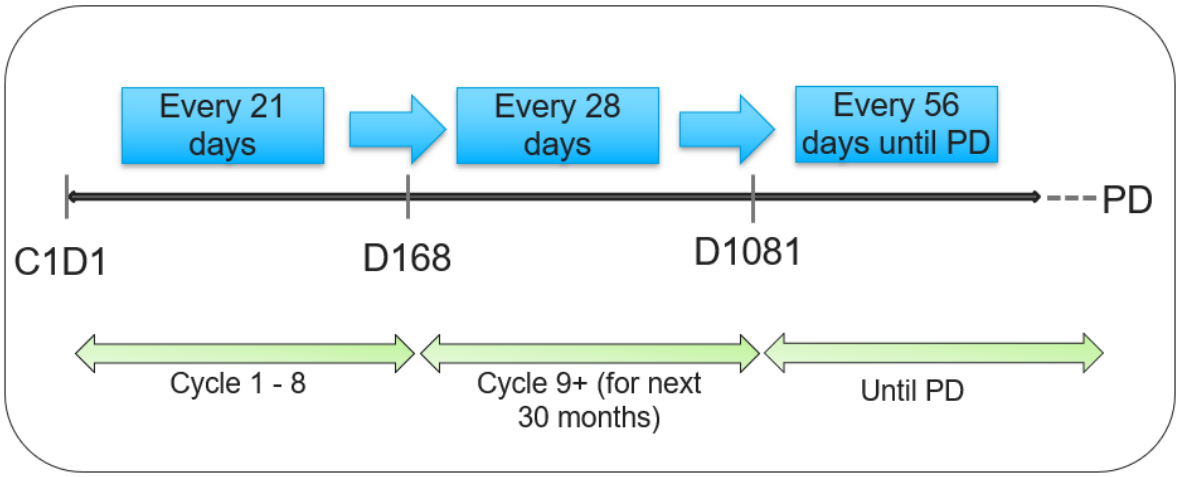
For this study, a new ADaM dataset has been programmed to identify missing Disease Evaluations (DE) based on DEs done at specific timepoints as specified by protocol; subsequent DEs are adjusted from actual last DE visit. For example, if disease evaluation visit 5 is delayed, and all subsequent visits are on schedule relative to visit 5, the updated scheduling would not flag later visits as out of window. This dataset was conceived during the pandemic as a tool to assess the impact of missing DEs and exposure on the study. This dataset forms the source of information that are needed to compute 2 or more consecutive missed DE.

IMPUTATION FOR MISSING DE

Imputation is based on the time elapsed between two actual disease evaluation visits.

- Impute 1 missing DE if time elapsed is > 2x and ≤2.5x frequency
- Impute 2 missing DE if time elapsed is > 2.5x and ≤3.5x frequency
- Impute 3 missing DE if time elapsed is > 3.5x and ≤4.5x frequency

and so on so forth. Where frequency is the frequency of scheduled disease evaluation for that cycle. So, for cycle 1 to cycle 8, the frequency of DE is every 3 weeks (21 days). For cycle 9 onwards up to next 30 months, it is every 4 weeks (28 days) and thereafter every 8 weeks (56 days) until PD.



PARAMETERS COMPUTED

The parameters of interest are:

- Number of missing DE
- Missed at least 1 DE
- Missing 2 or more DE
- Missing 2 or more consecutive DE
- In the time of the COVID-19 pandemic, the analyses needed to be adjusted to quantify the impact of the pandemic on the ongoing clinical trials

Together with PFS information, the parameter “Missing 2 or more consecutive DE” constitutes the QTL parameter.

CALCULATION FOR QTL THRESHOLD

$$\frac{\#\ of\ subjects\ with\ \geq 2\ consecutive\ DE\ followed\ by\ PFS}{total\ \#\ of\ PFS\ event}$$

As of July 2022, this is well below the secondary threshold.

CONCLUSION

Root Cause analysis revealed that the two most common reason for missing DEs in this study are i) misalignment of DE schedule with treatment visit and ii) site closure due to Covid. Robust mitigation plan was put in place such as updating a visit calculator based on near real time data to track potential missed evaluation or even delays. Allowing local labs to perform DE during pandemic was another one.
Identifying critical to quality data early in the process is paramount to address systematic issue in the study. Regular interaction between different functions can vastly improve monitoring strategy and mitigate potential risks. Even if a threshold is not breached or not likely to be breached in near

future, still a robust monitoring mechanism should be put in place. Finally, in case a breach occurs, a statistical programmer is called upon to provide additional data support in the form of various analysis outputs along with a summary of important deviations and action taken in CSR.

REFERENCES AND ACKNOWLEDGEMENT

1. Quality Tolerance Limits: Framework for Successful Implementation in Clinical Development – Ruma Bhagat et al *Therapeutic Innovation and Regulatory Science (2021)*

2. Acknowledgement to Jim Wang, Compound Lead Statistician for statistical inputs, Janssen R&D

APPENDIX 1: EXAMPLE OF THE NEW ADAM

Impute missed DE

SUBJID	AVISIT	AVISITN	ADT	ADY	ASTDT	AENDT	VISIT	VISITNUM	PARAMCD	AVALC	AVALCAT1
100001	DISEASE EVALUATION 1	400001	13-Dec-18	1	06-Dec-18	20-Dec-18	DISEASE EVALUATION 1	400001	MCLPA	AT SITE	DONE
100001	DISEASE EVALUATION 2	400002	03-Jan-19	22	27-Dec-18	10-Jan-19	DISEASE EVALUATION 2	400002	MCLPA	AT SITE	DONE
100001	DISEASE EVALUATION 2.1	400002.1	24-Jan-19	43	17-Jan-19	31-Jan-19			MCLPA	MISSED	NOT DONE
100001	DISEASE EVALUATION 3	400003	15-Feb-19	65	08-Feb-19	22-Feb-19	DISEASE EVALUATION 3	400003	MCLPA	AT SITE	DONE
100001	DISEASE EVALUATION 4	400004	08-Mar-19	86	01-Mar-19	15-Mar-19	DISEASE EVALUATION 4	400004	MCLPA	AT SITE	DONE
100001	DISEASE EVALUATION 5	400005	29-Mar-19	107	22-Mar-19	05-Apr-19	DISEASE EVALUATION 5	400005	MCLPA	AT SITE	DONE
100001	DISEASE EVALUATION 6	400006	23-Apr-19	132	16-Apr-19	30-Apr-19	DISEASE EVALUATION 6	400006	MCLPA	AT SITE	DONE
100001	DISEASE EVALUATION 7	400007	09-May-19	148	02-May-19	16-May-19	DISEASE EVALUATION 7	400007	MCLPA	AT SITE	DONE
100001	DISEASE EVALUATION 8	400008	10-May-19	149	03-May-19	17-May-19	DISEASE EVALUATION 7	400007	MCLPA	AT SITE	DONE

Missed 2 or more consecutive DE

SUBJID	AVISIT	AVISITN	ADT	ADY	ASTDT	AENDT	VISIT	VISITNUM	PARAMCD	AVALC	AVALCAT1
100041	DISEASE EVALUATION 22	400022	18-Aug-20	540	11-Aug-20	25-Aug-20	DISEASE EVALUATION 22	400022	MCLPA	AT SITE	DONE
100041	DISEASE EVALUATION 23	400023	15-Sep-20	568	08-Sep-20	22-Sep-20	DISEASE EVALUATION 23	400023	MCLPA	AT SITE	DONE
100041	DISEASE EVALUATION 24	400024	13-Oct-20	596	06-Oct-20	20-Oct-20	DISEASE EVALUATION 24	400024	MCLPA	AT SITE	DONE
100041	DISEASE EVALUATION 24.1	400024.1	10-Nov-20	624	03-Nov-20	17-Nov-20			MCLPA	MISSED	NOT DONE
100041	DISEASE EVALUATION 24.2	400024.2	08-Dec-20	652	01-Dec-20	15-Dec-20			MCLPA	MISSED	NOT DONE
100041	DISEASE EVALUATION 24.3	400024.3	05-Jan-21	680	29-Dec-20	12-Jan-21			MCLPA	MISSED	NOT DONE
100041	DISEASE EVALUATION 25	400025	26-Jan-21	701	19-Jan-21	02-Feb-21	DISEASE EVALUATION 25	400025	MCLPA	AT SITE	DONE
100041	DISEASE EVALUATION 26	400026	09-Feb-21	715	02-Feb-21	16-Feb-21	DISEASE EVALUATION 26	400026	MCLPA	AT SITE	DONE
100041	DISEASE EVALUATION 27	400027	09-Mar-21	743	02-Mar-21	16-Mar-21	DISEASE EVALUATION 27	400027	MCLPA	AT SITE	DONE
100041	DISEASE EVALUATION 28	400028	06-Apr-21	771	30-Mar-21	13-Apr-21	DISEASE EVALUATION 28	400028	MCLPA	AT SITE	DONE

APPENDIX 2: EXAMPLE OF MISSED DE FOLLOWED BY DEATH/ PD

Missed 2 or more consecutive DE followed immediately by PD

SUBJID	AVISIT	DATE	RESULT	PD DATE
100164	DISEASE EVALUATION 14	06-Mar-20	DONE	29-May-20
100164	DISEASE EVALUATION 14.1	03-Apr-20	NOT DONE	29-May-20
100164	DISEASE EVALUATION 14.2	01-May-20	NOT DONE	29-May-20
100164	DISEASE EVALUATION 15	29-May-20	DONE	29-May-20

Missed 2 or more consecutive DE followed immediately by death

SUBJID	AVISIT	DATE	RESULT	Death DATE
100437	DISEASE EVALUATION 2	27-Aug-19	DONE	22-Nov-19
100437	DISEASE EVALUATION 3	16-Sep-19	DONE	22-Nov-19
100437	DISEASE EVALUATION 3.1	07-Oct-19	NOT DONE	22-Nov-19
100437	DISEASE EVALUATION 3.2	28-Oct-19	NOT DONE	22-Nov-19

APPENDIX 3: STUDY POWER AND/ OR CCO

True HR	Different CCO for primary MRD cut	Projection with censoring events after missing ≥ 2 consecutive DEs					
		5% of all new events		10% of all new events		20% of all new events	
		Expected PFS events #	Power to show HR<0.85	Expected PFS events #	Power to show HR<0.85	Expected PFS events #	Power to show HR<0.85
0.63*	Apr2021	78	91%	76	90%	73	90%
	Jan2021	70	90%	68	89%	65	89%
	Oct2020	60	88%	59	88%	57	87%
0.70	Apr2021	78	80%	76	80%	73	80%
	Jan2021	70	79%	68	79%	65	78%
	Oct2020	60	77%	59	77%	57	77%
0.75	Apr2021	78	71%	76	71%	73	70%
	Jan2021	70	70%	68	70%	65	69%
	Oct2020	60	69%	59	69%	57	68%

- Delay the CCO for the primary MRD cut by 3-6 months that allows to accumulate more PFS events due to the censoring above
- Historic data: 4%- 6% such censored events in two previous similar trials.

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