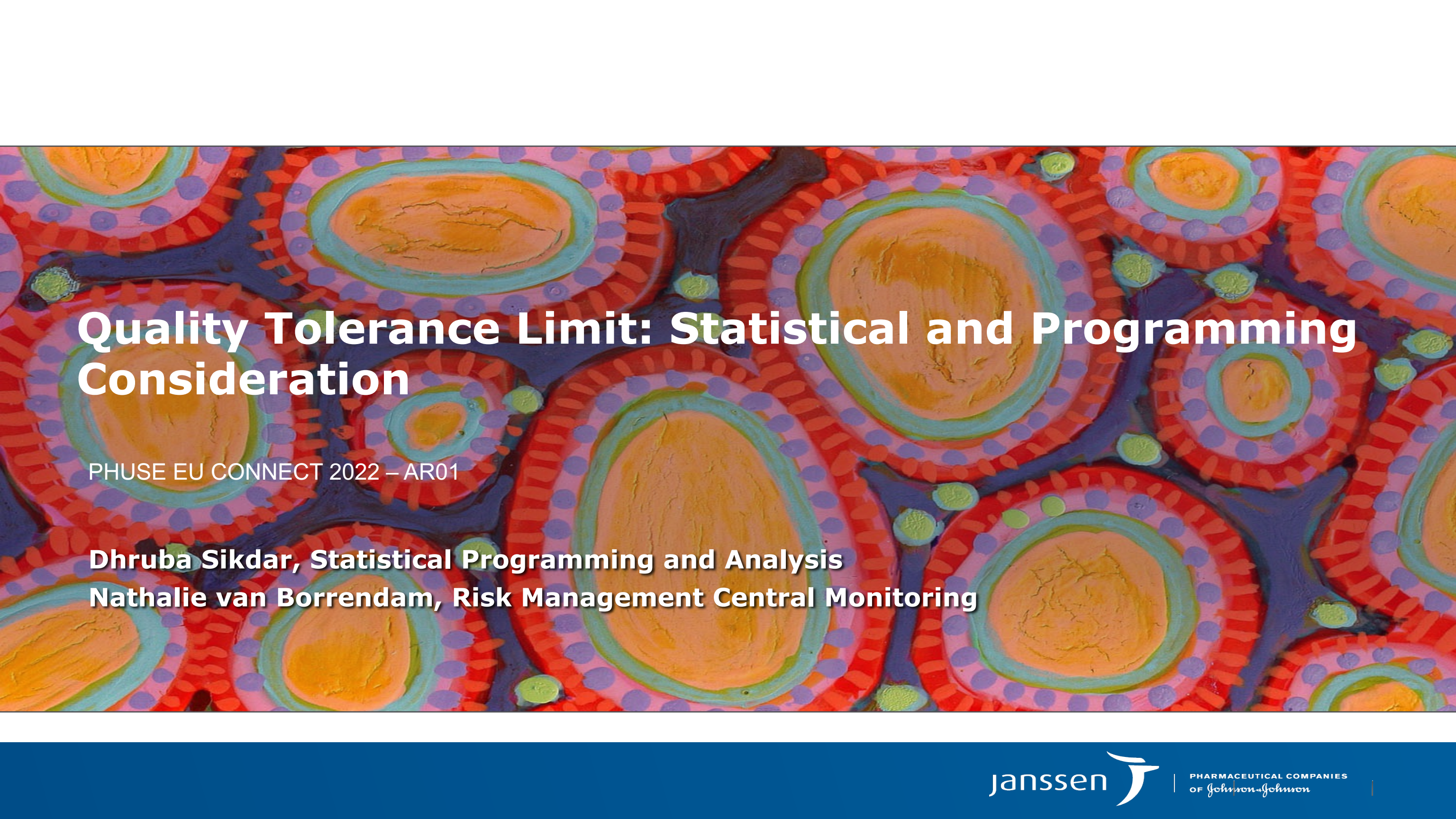




Quality Tolerance Limit: Statistical and Programming Consideration

PHUSE EU CONNECT 2022 – AR01

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Agenda

- QTL – A brief Background
- QTL Process – Role of Statistician and Statistical Programming
- QTL Implementation – A Case Study from A Phase 3 Oncology Trial
- Conclusion
- Q&A

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QTL – Brief Background

ICH E6 R2 requires the establishment of QTLs to “*identify systematic issues that can impact subject safety or reliability of trial results*” and ensure that important deviations from the predefined QTLs and associated remedial actions taken are reported in the Clinical Study Report (CSR)

Section 5.0.4 – Risk Control: “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. Risk reduction activities may be incorporated in protocol design and implementation, monitoring plans, agreements between parties defining roles and responsibilities, systematic safeguards to ensure adherence to standard operating procedures, and training in processes and procedures.

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 systematic 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”.**

Section 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).”

What is a QTL?



A **parameter** is a **variable** related to Critical to Quality element assessed at **trial level**.

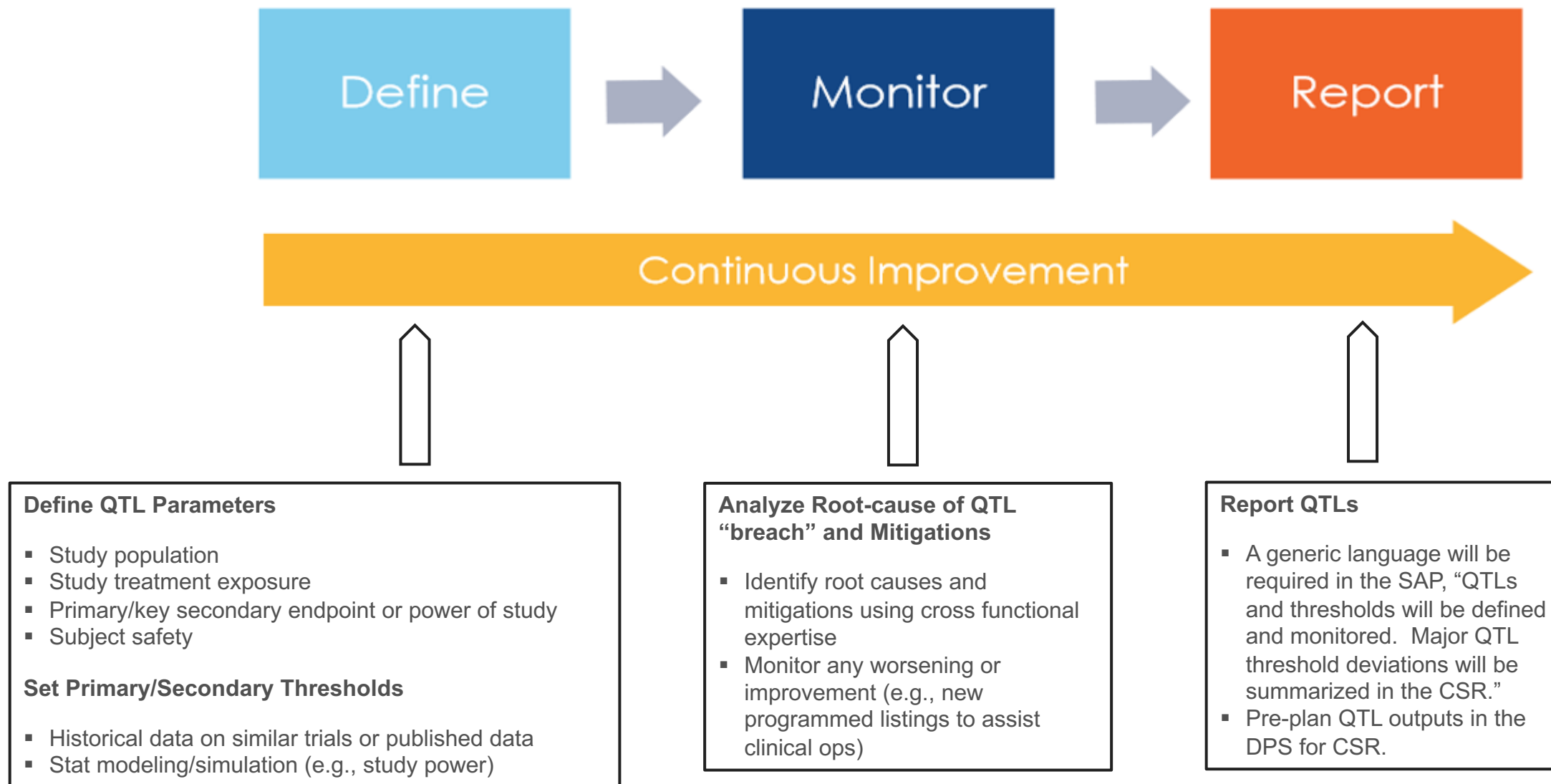
A **threshold associated with parameter** are designed to detect potential issues that **could impact participants' safety or reliability of trial results and that could be mitigated**. If a threshold is reached or exceeded, an appropriate action is taken.

QTL Process



“QTL Core Team”: GTL, Statistician, Clinician (SRP), CM, Statistical Programmer

QTL Process - Involvement of Statisticians

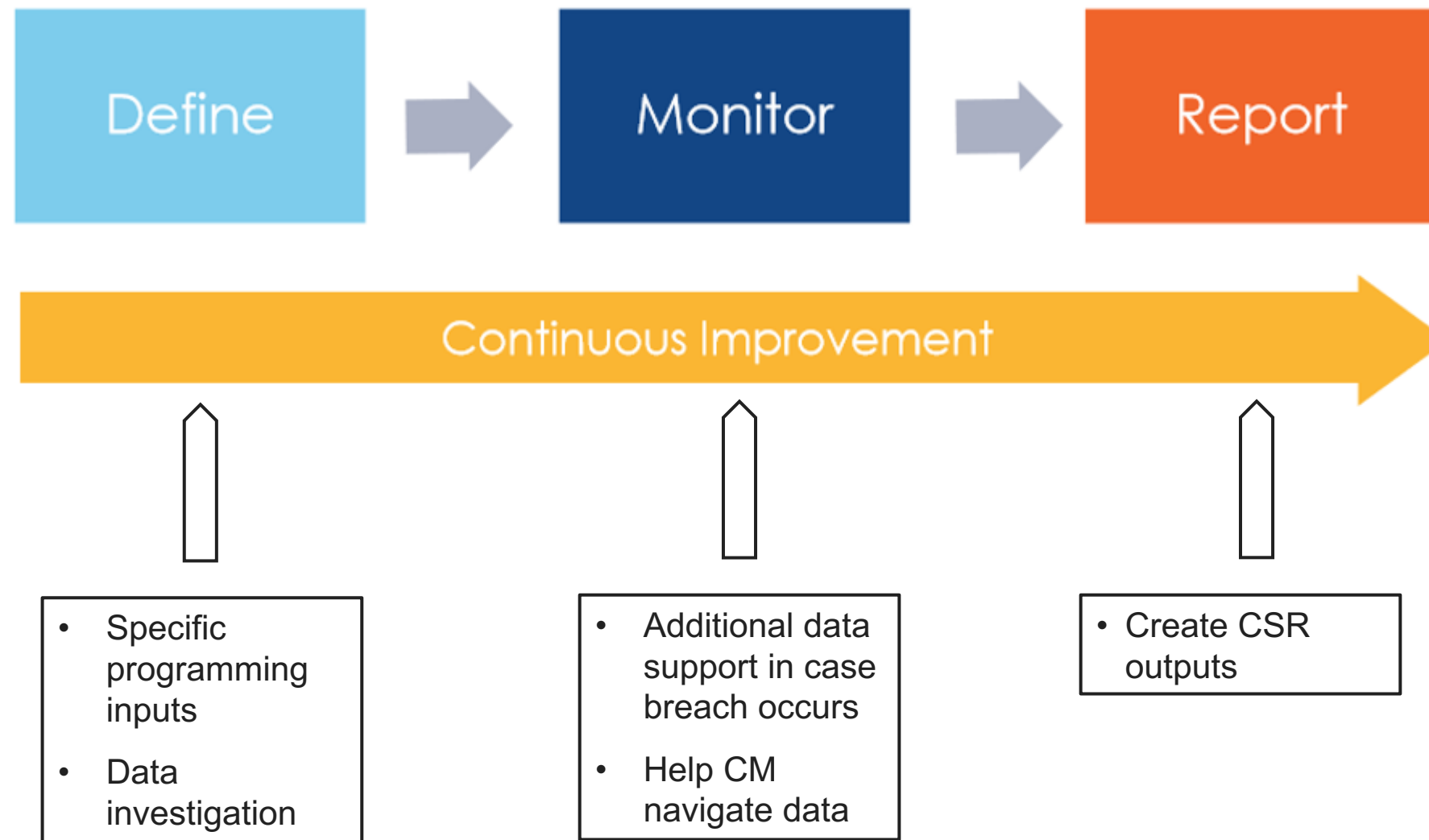


Some Statistical Principles Guiding QTL

At Define Stage

- What is the Primary Objective
- Key question the trial is trying to answer
- What is the analysis plan as specified in SAP
- What is the most Critical to Quality Data
- iARBM Plan
- Key Risk Indicators (KRIs)
- May want to link Primary/Secondary Objective with QTL Parameters
- To determine QTL Threshold:
 - Simulate study data to analyse different scenarios to evaluate impact on the power of the study.
 - Consult historical data from similar studies

QTL Process - Involvement of Statistical Programming



QTL Implementation: A Case Study from A Phase 3 Oncology Trial

Skin cells at 20x magnification

QTL Implementation – A Phase 3 Oncology Trial

- The Trial
 - Randomized open label, multicentre phase 3 study evaluating subjects with newly diagnosed multiple myeloma
- Secondary Objective
 - Key secondary objective – PFS (critical to quality)
- N = 360 patients
 - Fully enrolled
 - Actual N=395 patients, Alpha=0.05, 80% power
- Key secondary endpoint- PFS
 - 80% power assuming HR=0.63 (improving median PFS from 43 to 68 months)

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 – Dedicated ADaM Dataset

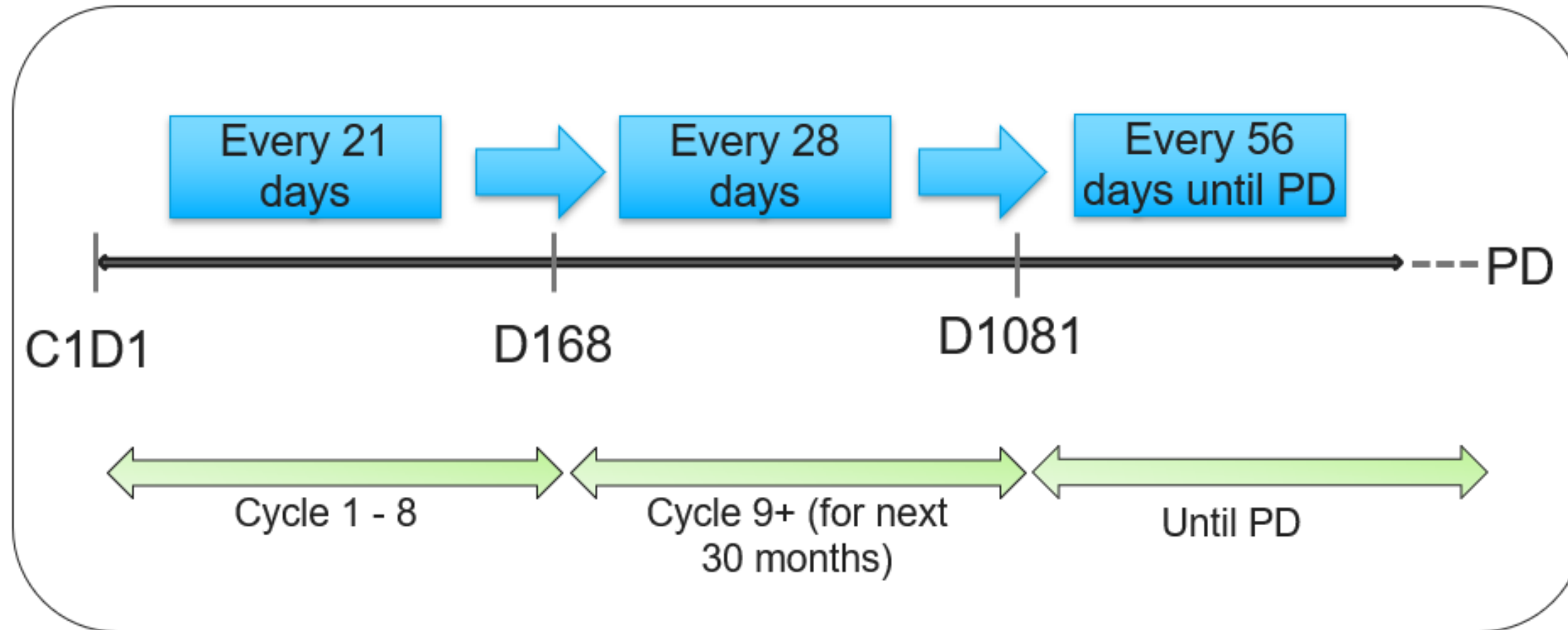
A dedicated ADaM – Computing 2 or more consecutive missed DE

- Based on DE done at specific timepoint as specified in Protocol
- Conceived during pandemic as a tool to assess the scope of missing disease evaluations or assessments (due to and not due to COVID)
- Feed into QTL dashboard. Helped in other analyses too.
- Together with PFS information it computes ≥ 2 consecutive missed DE followed by PFS events.

Imputation for missing DEs

- Imputation based on the time between visits:
 - Impute 1 missing if time elapsed is $>2x$ and $\leq 2.5x$ the frequency
 - Impute 2 missing if time elapsed is $>2.5x$ and $\leq 3.5x$ the frequency
 - Impute 3 missing if time elapsed is $>3.5x$ and $\leq 4.5x$ the frequency
 - ...
- Cycle 1-8, DE every 3 weeks (21 days); C1D1 - 168 days (8×21)
- Cycle 9+ for next 30 months, DE every 4 weeks (28 days); 168 Days – 1081 days ($168 + 30 \times 30.44$)
- Thereafter every 8 weeks (56 days) until PD; > 1081 days
- Include CCO date (or earliest of PD, death, trial discontinue, subseq therapy) as a cut off for imputing missing visits

Imputation for missing DEs



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.

QTL Threshold Calculation

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

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

Conclusion

- Root cause analysis and mitigation strategies for missing DEs
 - ❖ DE schedule is not aligned with treatment visit that led to incorrect DE tracking by the sites
 - ❖ Site closure due to COVID
 - ❖ Visit calculator based on near real time data to track potential delayed/missed DEs
 - ❖ Allow local labs for DEs during the pandemic
- Very much collaborative effort between different functions (CM, Stats, Programming, ..)
- Identify critical to quality data early in the trial.
- Good to have a second QTL parameter.
- Constant monitoring needed even if the QTL is not breached.
- In case of a breach, be prepared to step in with additional data support.

Reference 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

Questions?

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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