

Interactive Session:

Quality Tolerance Limits (QTLs): Setting the Threshold

– SHARE, DO, LEARN

PHUSE Working Group QTL Thresholds

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QTL Threshold Working Group



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QTL Threshold Working Group

Acknowledge the following working group team members for their active contribution to this interactive session:

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- Steven A. Gilbert - Senior Director Statistics – *Pfizer*
- Jim Wang - Associate Director – *Janssen R&D*
- Steve Young - Chief Scientific Officer – *CluePoints Inc.*
- Marta Kozinska - Director Centralized Monitoring – *AstraZeneca*
- Paula Rowley - Project Coordinator – *PHUSE*



Quality Tolerance Limits: Setting the Threshold – SHARE, DO, LEARN

The added value Quality Tolerance Limits bring depend on setting meaningful thresholds. During this session we will:

- SHARE- We will share real pharmaceutical industry experiences of methodologies used to set thresholds as well as QTL Statistical and Programming considerations
- DO – During hands-on activities you will have the opportunity to go through an exercise of setting a threshold, comparing methodologies and discuss best approaches
- LEARN – By sharing and doing the intent is to learn from each other. This will help drive the implementation of meaningful QTLs in the industry.

This session has a focus on the statistical elements of QTLs and the output of the workshop will be included in the White paper guidance for setting QTL threshold methodologies



Terminology

We speak about **study level** issues.

- Identifying the monitoring variable used to follow-up on the evolution of a risk during the trial. This shall be referred to as *defining the QTL parameter* for this Working Group.
- Identifying the threshold for this monitoring variable that separates the area of acceptable from the area of non-acceptable risk. This shall be referred to as *defining the QTL threshold* for this Working Group. (**primary limit** vs. secondary limit)



SHARE

Critical Quality Factor	QTL Parameter(s)	Scientific Rationale	Derivation of QTL Threshold
Data Integrity: Primary Endpoint	• (Annual) drop out rate. • Proportion of patients censored. • Proportion of patients that discontinued treatment.	• Ensure statistical power. • Avoid dilution of effect size. • Avoid prolongation of study.	• Simulation study. • Statistcial considerations for Primary Endpoint.
Data Integrity: Efficacy Data	• Proportion of patients LTF. • Proportion of patients that discontinued treatment.	• Reliability of treatment assessment. • Correct baseline assessment.	• Expert knowledge/ expectations. • Expectations from historical data.
Compliance: Patients	• Proportion of patients missing In/Ex-criteria.	• Ensure understanding of protocol/scientific rationale. • Ensure correct study population.	• Expectations from historical data.
Compliance: Treatment	• Proportion of patients without any intake of study medication.	• Robust ITT population for analysis.	• Expectations from historical data.



QTL – Let's DO it!

Therapeutic Area: Dermatology

Study Name: **QT-Lotion**

Study Details: Blinded, randomized controlled study, comparing the application of PHUSE-Blend with standard care over the period of 12 months
Phase III

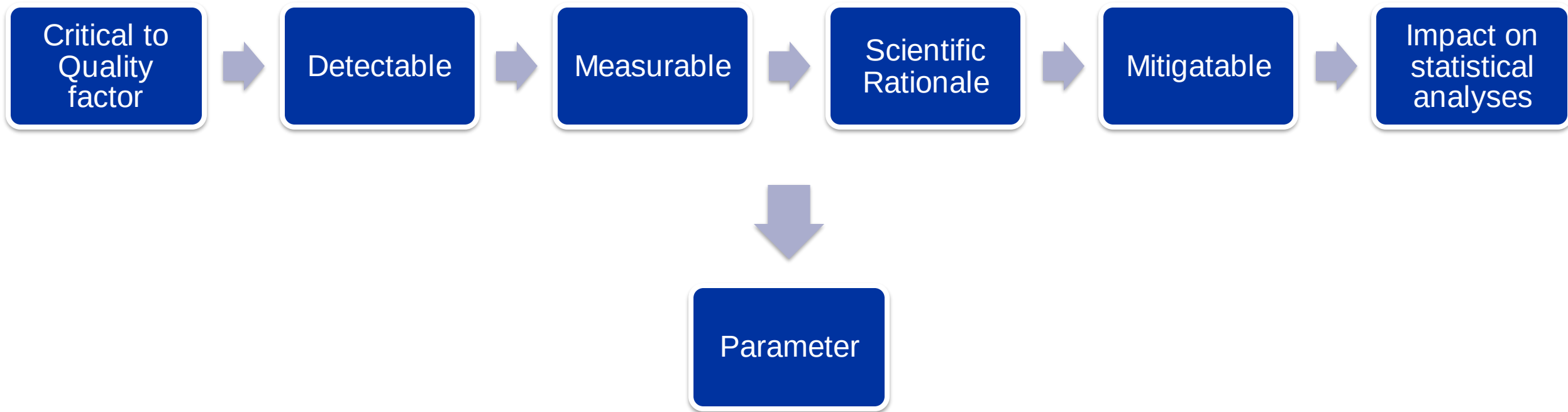
Primary Endpoint: Change from baseline (in %) PASI 90 Response after 52 weeks

Study Specifics

- 700 patients, at least 18 - 65 years old
- Study data is collected via tablet



QTL Parameter



QTL – Parameter Identified

QTL parameters for *QT-Lotion* study



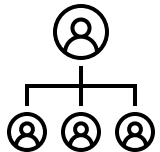
- Number of patients that discontinue trial



- Change in tube weight compared to target



- Number of missing site visits per patient



- Number of different raters per patient



QTL – Historical Study

Therapeutic Area: Dermatology

Study Name: **ConPHUSEd**

Study Details: Blinded, randomized controlled study comparing the application of PHUSE-Blend with standard care over the period of 12 months
Phase III

Primary Endpoint: Change from baseline (in %) PASI 90 Response after 52 weeks

Study Specifics

- 650 patients, at least 18 – 49 years old
- Study data is collected via tablet



ConPHUSEd: Treatment Exposure



Critical to Quality Factor: Treatment Exposure

QTL Parameter: Number of patients that discontinued trial

Historical data: Cumulative number of patients that left study over time

QT-Lotion: QTL Threshold

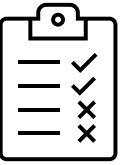
Data showing the number and timepoints of patients dropping out of ConPHUSEd study were collected.

The QT-Lotion team wants to keep the maximum drop out rate at the level of the ConPHUSEd drop out rate.

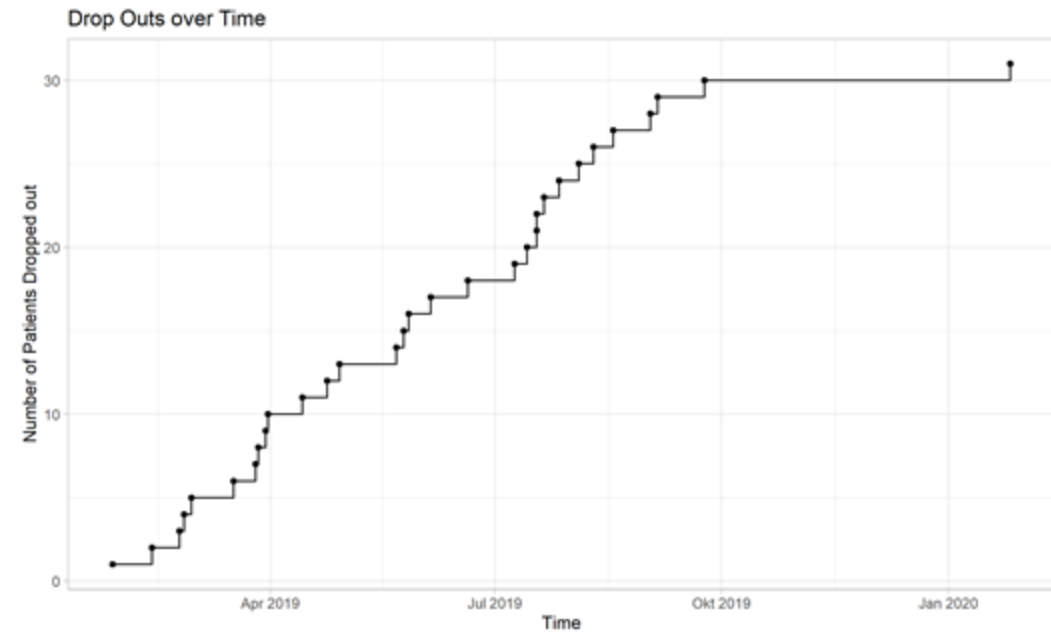
What QTL threshold do you propose?

- (1) A maximum drop-out rate of 5% for the complete study period.
- (2) A maximum drop-out rate of 2.5% for the first half of the study – and a maximum drop-out rate of 5% for the second half of the study.
- (3) A maximum drop-out rate of 5% for the complete study – but in addition a Warning Limit / Secondary limit for the first half of the study will be set at 2.5%.

ConPHUSEd: Treatment Exposure

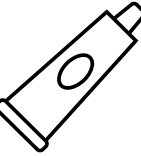


Dropout Date	Days since FPI	Cumulative Number of Patients dropped out	Cumulative Proportion [%] of Patients dropped out
2019-01-27	25	1	0.15
2019-02-12	41	2	0.31
2019-02-23	52	3	0.46
2019-02-25	54	4	0.62
2019-02-28	57	5	0.77
2019-03-17	74	6	0.92
2019-03-26	83	7	1.08
2019-03-27	84	8	1.23
2019-03-30	87	9	1.38
2019-03-31	88	10	1.54
2019-04-14	102	11	1.69
2019-04-24	112	12	1.85
2019-04-29	117	13	2
2019-05-22	140	14	2.15
2019-05-25	143	15	2.31
2019-05-27	145	16	2.46
2019-06-05	154	17	2.62
2019-06-20	169	18	2.77
2019-07-09	188	19	2.92
2019-07-14	193	20	3.08
2019-07-18	197	21	3.23
2019-07-18	197	22	3.38
2019-07-21	200	23	3.54
2019-07-27	206	24	3.69
2019-08-04	214	25	3.85
2019-08-10	220	26	4
2019-08-18	228	27	4.15
2019-09-02	243	28	4.31
2019-09-05	246	29	4.46
2019-09-24	265	30	4.62
2020-01-26	389	31	4.77





ConPHUSEd: Treatment Compliance

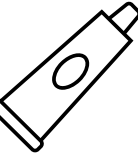


Critical to Quality Factor: Treatment Compliance

QTL Parameter: Change in tube weight compared to target

Historical data:

- (1) Change in Tube Weight compared to Target by Visit
- (2) Change in Tube Weight compared to Target across study
- (3) Number of times patients applied to much/to less of medication



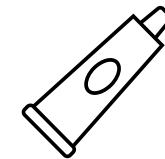
The ConPHUSEd study collected data on patients' treatment compliance. Based on this data, QTL thresholds will be derived for the QT-Lotion study.

What do you consider an acceptable margin for meeting the targeted dose for the QT-Lotion study?

- (1) +/-20%.
- (2) +/-30%.
- (3) I don't know. I am ConPHUSEd.



ConPHUSEd: Treatment Compliance



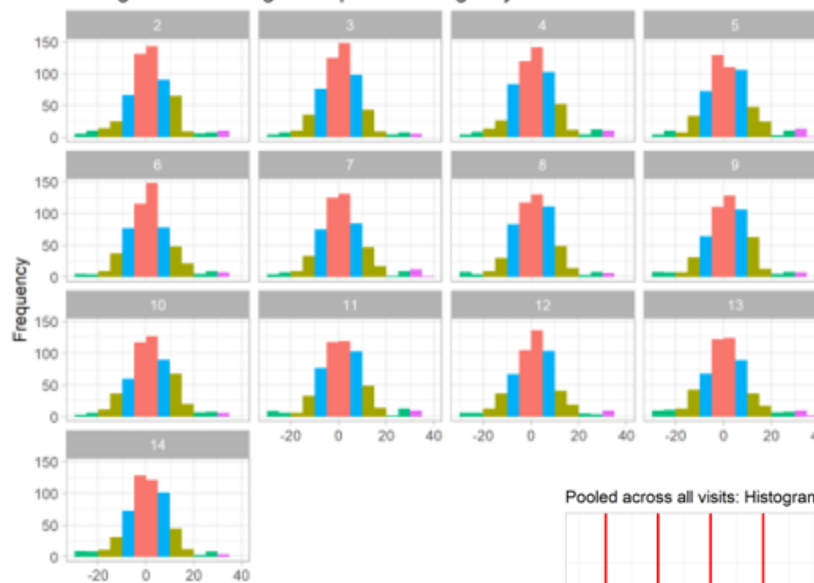
Number of Patients by Visits and Range of Deviation from Targeted Dose

Visit Number	Number of Patients within Range - by Visit				
	at most 5%	between 5% and 10%	between 10% and 20%	between 20% and 30%	more than 30%
2	274	156	113	28	10
3	273	174	97	22	5
4	260	185	102	28	10
5	239	178	111	27	14
6	263	155	115	23	7
7	256	159	106	22	13
8	247	194	102	23	6
9	238	170	114	28	7
10	244	150	137	24	6
11	237	180	102	30	10
12	241	171	110	21	10
13	246	157	110	36	12
14	249	173	98	28	4

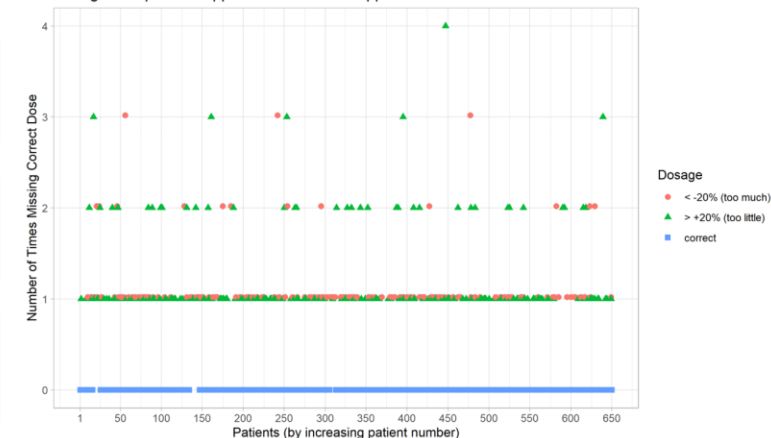
Proportion of Patient Visits by Visit and Range of Deviation from Targeted Dose

Visit Number	Cumulative Number of Patient Visits	Cumulative Patient Visits within Range - by Visit				
		at most 5%	between 5% and 10%	between 10% and 20%	between 20% and 30%	more than 30%
2	1231	22.26	12.67	9.18	2.27	0.81
3	1802	30.36	18.31	11.65	2.77	0.83
4	2387	33.81	21.58	13.07	3.27	1.05
5	2956	35.39	23.44	14.31	3.55	1.32
6	3519	37.2	24.1	15.29	3.64	1.31
7	4075	38.4	24.71	15.8	3.68	1.45
8	4647	38.99	25.84	16.05	3.72	1.4
9	5204	39.39	26.35	16.53	3.86	1.38
10	5765	39.79	26.38	17.29	3.9	1.35
11	6324	40.02	26.9	17.38	4.03	1.39
12	6877	40.31	27.22	17.58	4.01	1.43
13	7438	40.58	27.28	17.73	4.19	1.48
14	7990	40.89	27.56	17.73	4.26	1.43

Change of Tube Weight compared to Target by Visit

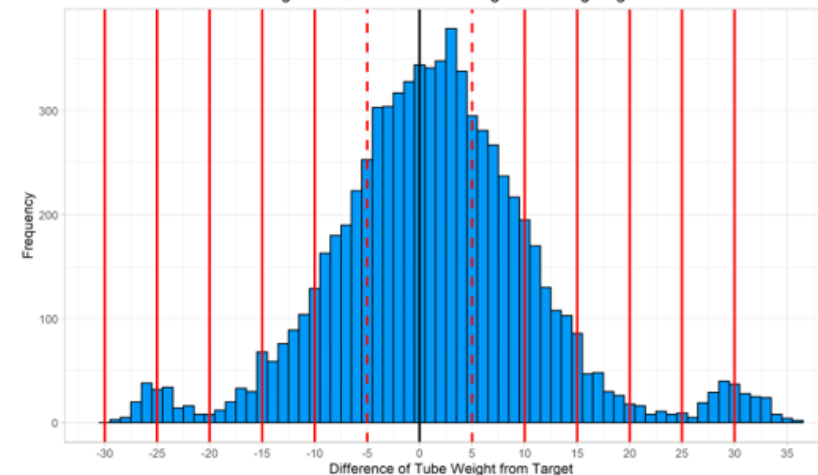


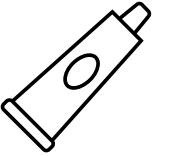
Dosage Compliance: Applied Too much vs. Applied Too little



Pooled across all visits: Histogram of Deviations from Targeted Dosing Regimen

Visit 2 to 14





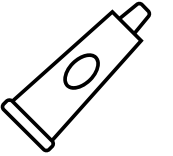
The ConPHUSEd study collected data on patients' treatment compliance. Based on this data, QTL thresholds will be derived for the QT-Lotion study.

Case A: The QT-Lotion trial team decides set up a QTL threshold focusing on the efficacy of the trial. That is, the number of times a patient is missing the targeted dose is considered. What QTL threshold would be appropriate?

- (1) A patient should not miss more than twice the targeted dose.
- (2) A patient should not miss more than three times the targeted dose.
- (3) The data of the ConPHUSEd trial does not provide enough information.



QT-Lotion: QTL Threshold



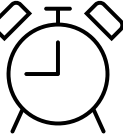
The ConPHUSEd study collected data on patients' treatment compliance. Based on this data, QTL thresholds will be derived for the QT-Lotion study.

Case B: The QT-Lotion trial team decides set up a QTL threshold focusing on the data integrity of the trial. That is, the number of patients missing the targeted dose is considered. What QTL threshold would be appropriate?

- (1) At most 2% of the patients could miss their targeted dose based on a +/-30% acc. margin.
- (2) At most 7% of the patients could miss their targeted dose based on a +/-20% acc. margin.
- (3) I propose a different approach.



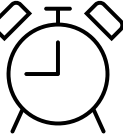
ConPHUSEd: Visit Compliance



Critical to Quality Factor: Patient Visit Compliance

QTL Parameter: Number of missing site visits per patient

Historical data: Number and time points of visits missed by patients



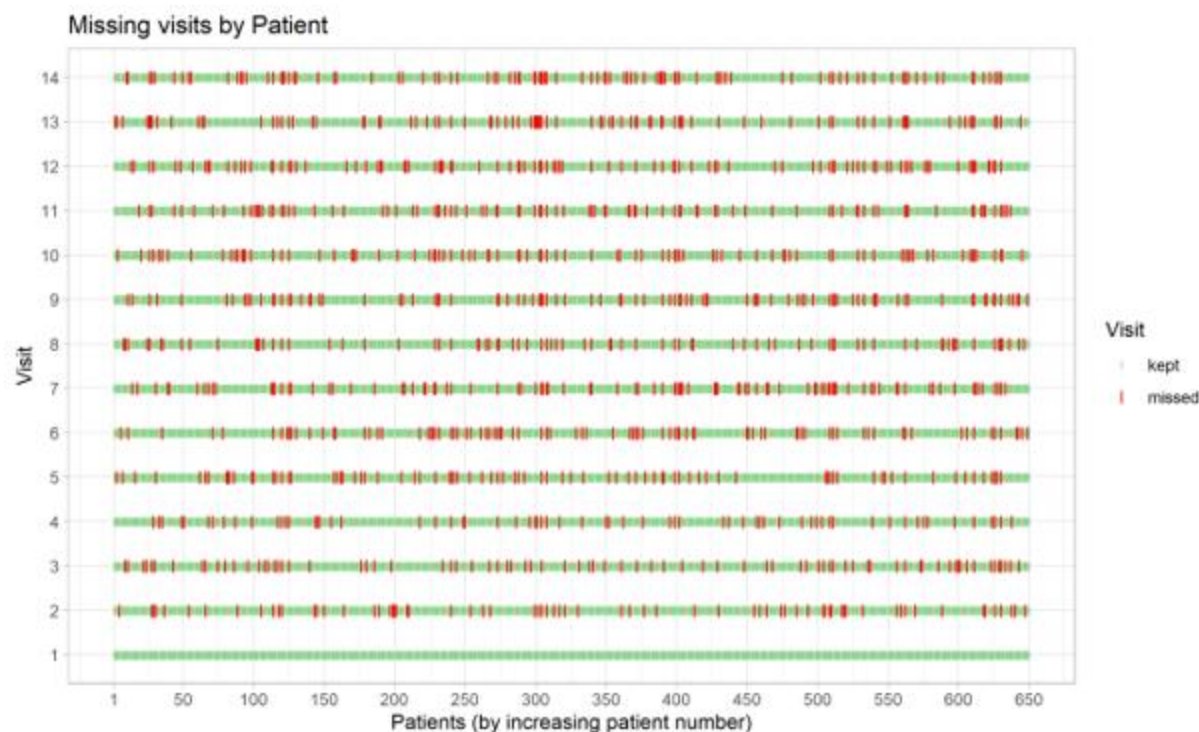
Data on missing patients visits was collected during ConPHUSEd study. During submission of the ConPHUSEd study, the meaningfulness of the data was challenged because of the high proportion of visits missed.

Therefore, the QT-Lotion study team wants to avoid the same discussion and aims for a lower proportion of missing visits. What does that mean for the derivation of a QTL threshold?

- (1) The QTL threshold for the QT-Lotion study will be set at 90% of the observed proportion of the ConPHUSEd study (12.5% of all patient visits) to account for a lower proportion of missing visits.
- (2) Aiming for a lower proportion, the ConPHUSEd data does not help to derive a QTL threshold for the QT-Lotion study. Experts on this topic shall be interviewed for an appropriate threshold.
- (3) I have an idea for a completely different approach other than (1) and (2).

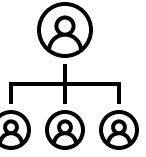
Proportion of Patient Visits missed

Visit	Number of Patient Visits	Number of Patients that missed Visit	Proportion [%] of Patients Visits missed	Cumulative Number of Patient Visits	Cumulative Proportion [%] of missed Patient Visits
1	650			650	0
2	581	69	11.88	1231	5.61
3	571	79	13.84	1802	8.21
4	585	65	11.11	2387	8.92
5	569	81	14.24	2956	9.95
6	563	87	15.45	3519	10.83
7	556	94	16.91	4075	11.66
8	572	78	13.64	4647	11.9
9	557	93	16.7	5204	12.41
10	561	89	15.86	5765	12.75
11	559	91	16.28	6324	13.06
12	553	97	17.54	6877	13.42
13	561	89	15.86	7438	13.61
14	552	98	17.75	7990	13.89





ConPHUSEd: Site Compliance



Critical to Quality Factor: Site Compliance

QTL Parameter: Number of different raters per patient

Historical data: Cumulative number of patients that left study over time

QT-Lotion: QTL Threshold

During the ConPHUSEd study it was observed that the number of raters per patient varied.

The QT-Lotion study team discussed implications of different central monitoring approaches and QTL thresholds.

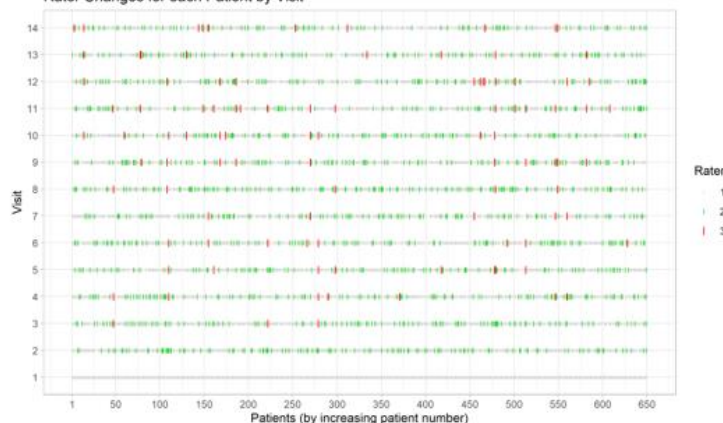
- (1) A QTL threshold for the total number of raters per patient should be implemented.
- (2) A QTL threshold for the total number of times the rater changed at subsequent visits should be implemented.
- (3) I do not consider *Number of Raters per Patient* a QTL parameter.

Number of Different Rater per Patient by Visit

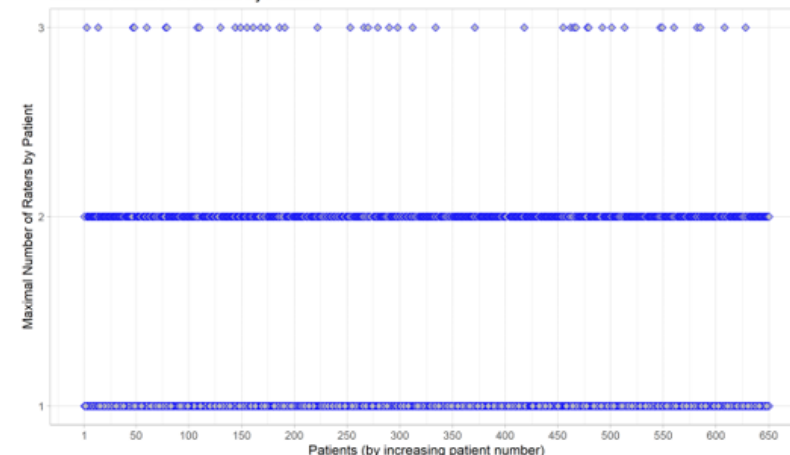
Visit	1 Rater	2 Raters	3 Raters
1	650		
2	530	120	
3	439	208	3
4	360	282	8
5	299	337	14
6	240	392	18
7	192	438	20
8	154	474	22
9	125	499	26
10	107	512	31
11	94	519	37
12	80	530	40
13	67	542	41
14	57	548	45

Displayed are the number of patients that had 1,2 or 3 different raters up to the specific visits.

Rater Changes for each Patient by Visit



Maximal Number of Raters by Patient

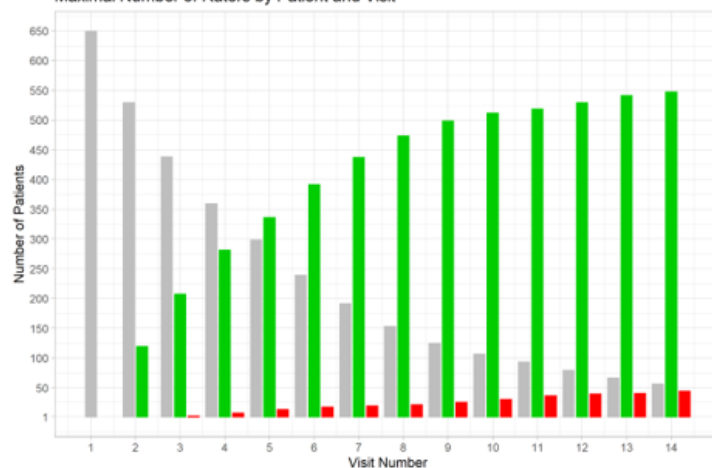


Number of Rater Changes

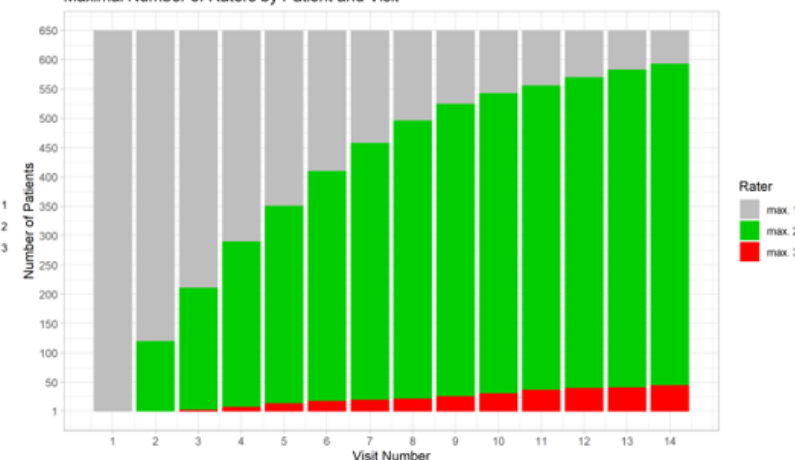
Visit	Number of Patients with Rater Changes										
	1 Change	2 Changes	3 Changes	4 Changes	5 Changes	6 Changes	7 Changes	8 Changes	9 Changes	10 Changes	11 Changes
1	650										
2	530	120									
3	439	129	82								
4	360	111	166	13							
5	299	89	222	32	8						
6	240	83	253	44	29	1					
7	192	76	274	46	56	5	1				
8	154	67	267	70	73	13	6				
9	125	48	272	68	98	28	9	2			
10	107	26	265	71	125	29	24	1	2		
11	94	23	233	65	154	33	35	10	3		
12	80	24	214	55	153	55	53	4	11	1	
13	67	18	196	53	163	46	85	10	10	2	
14	57	16	172	49	175	43	106	14	13	3	2

Displayed are the number of patients for which the rates changed through visits. E.g., a patient with Rater A at Visit 1, Rater B at Visit 2 and again Rater A at Visit 3 would have three changes.

Maximal Number of Raters by Patient and Visit



Maximal Number of Raters by Patient and Visit



QT-Lotion: QTL Threshold

During the ConPHUSEd study it was observed that the number of raters per patient varied.

Case A: A QTL threshold for the total number of raters per patient should be implemented.

- (1) There should be not more than two raters per patient.
- (2) There should be not more than three raters per patient.
- (3) I propose a different approach.

QT-Lotion: QTL Threshold

During the ConPHUSEd study it was observed that the number of raters per patient varied.

Case B: A QTL threshold for the total number of times the rater changed at subsequent visits should be implemented.

- (1) There should be not more than four rater changers per patient.
- (2) The number of changes is irrelevant as on the baseline visit and the last visit data are important for the Primary Endpoint evaluation.
- (3) I propose a different approach.

Thank you

PHUSE Working Group QTL Thresholds

Any further Comments/Suggestions/Question

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Groups**

