QUALITY TOLERANCE LIMITS VS. KEY RISK INDICATORS

1

QTL

- **Process driven**
- Setting of tolerance range for expected quality
- Focused on systematic issues
- Early identification of problematic trends
- Using medical & statistical knowledge
- Non-zero tolerance limits
- Usually 4-6 company wide
- Reportable

- Examples:
  - High % of randomized subjects not meeting PP population criteria
  - High % of subjects with premature drug discontinuation
  - High % of LFU subjects

KRI

- **Risk driven**
- Establishing parameters of risk
- Leading / lagging
- Focused on issues on a site-by-site basis or across a specified period of time
- Defined at risk-entity level
- Tailored to individual trial/therapy
- Usually 15-20 per trial
- Non-reportable

- Examples:
  - High % of missing CRF entries
  - Low % of queries resolved within time
  - Low number of enrolled patients

2

QTL CREATION, MONITORING, ANALYZING AND REPORTING

MAKING MODEL OF TYPICAL OR DESIRABLE PROCESS OF A CLINICAL TRIAL

CALCULATING CONTROL LIMITS OF THE EXPECTED MEASUREMENTS OF THE OUTPUT

COMPARING THE PROCESS DATA OF THE CONTROL LIMITS

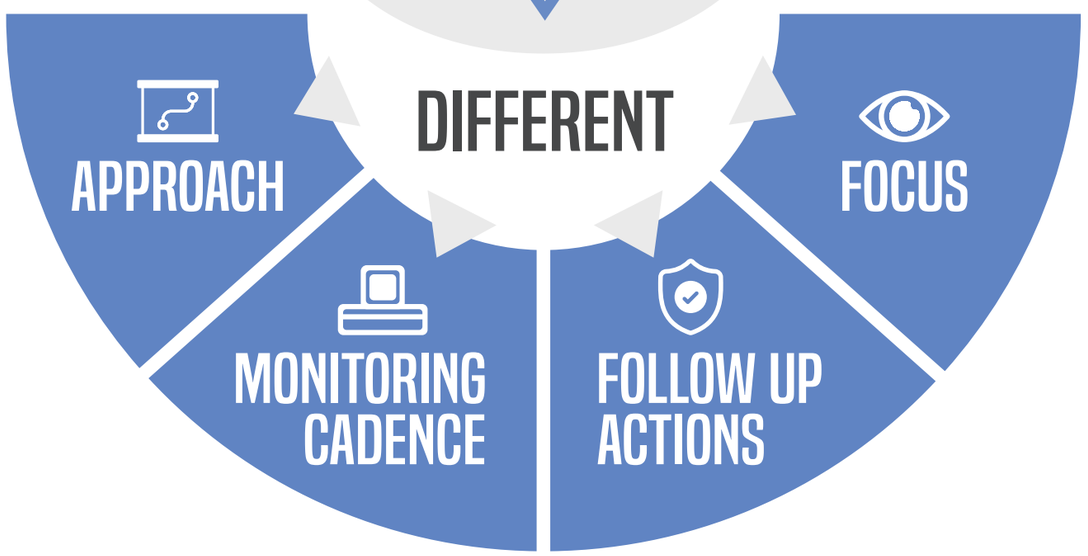
CSR

- Frequency of monitoring for each parameter
- Number of times the QTLs were exceeded
- Summary for each mitigation
- Summary of root causes of excursions
- Explanation of justification in case of adapting a new QTL during the study

3

QTL VS. KRI

SAME VARIABLES DIFFERENTLY EVALUATED



4

EXAMPLE OF USING QTL AND KRI FOR SAME VARIABLE

Number of “miss-randomized” patients or randomized patients who do not meet the study inclusion/exclusion criteria - is a KRI with zero threshold.
However, miss-randomization can not be 100% avoidable, especially for studies with rapid enrollment timelines. For this reason, a QTL should be established to assess miss-randomized patients. In case the QTL's threshold is exceeded, follow-up actions may be needed at multiple sites or multiple studies. In contrast - a single KRI may not evaluate a historical site issue or company-wide problem.

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