

The Importance of Being Ernest

– The role of QTLs in QbD

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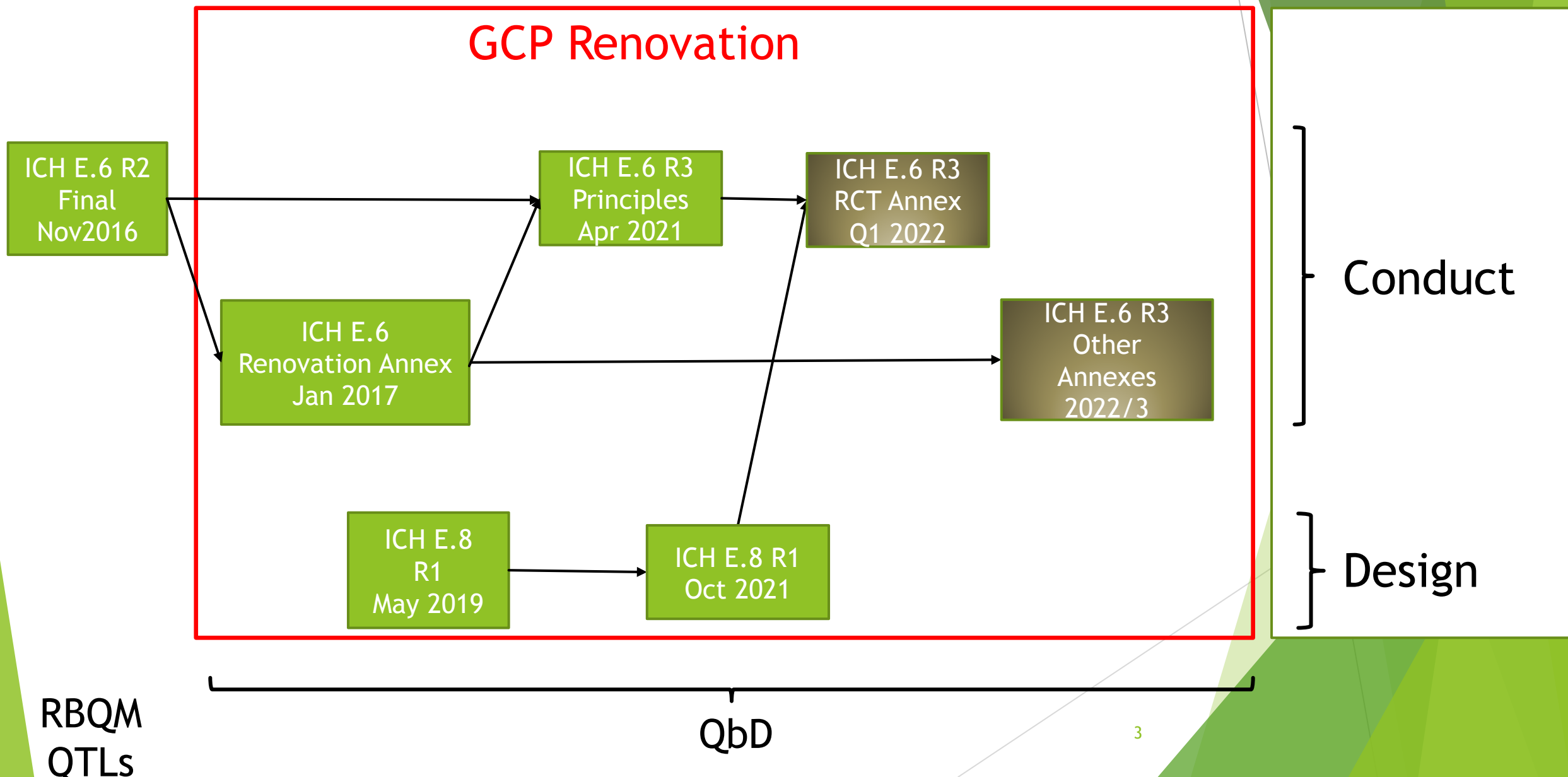
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Topics

- ▶ Background to ICH E6 R2
 - ▶ Regulatory
 - ▶ Structural
 - ▶ Issues that led to changes
- ▶ QTLs
- ▶ QbD
- ▶ Overcoming initial hurdles

Regulatory path



Drivers for ICH E.6 Addendum changes (CTTI Aug 2011)

- ▶ Concerns over quality from Regulatory Authorities
 - ▶ Lack of trust for ICH-GCP statements in submission based on Audits
 - ▶ We claim “all trials conducted to ICH-GCP”, but results from inspections always show GCP issues
 - ▶ Upset over lack of transparency
 - ▶ Want defined quality
 - ▶ Transparency
 - ▶ Want “Quality by Design, sometimes feel it is by Accident”
 - ▶ Industry is too silo'd, this impacts Quality
 - ▶ Lack of demonstrable oversight
 - ▶ Do not understand risk
 - ▶ Poor “Root cause analysis”
 - ▶ “Stupidity of 100% SDV” as solution, CRA misses “helicopter” view of site
 - ▶ Pharma is wasting resources

What is Quality by Design (QbD)

- ▶ Is similar to PDSA cycle used iteratively
 - ▶ PDSA=Plan-Do-Study-Act
- ▶ Focuses on risk based approaches
 - ▶ Not just Risk Based Monitoring
- ▶ Encourages Continuous Quality Improvement
 - ▶ An essential part of the clinical development QbD
- ▶ Intention to design reproducible (capable) processes
- ▶ Measured quality
- ▶ Documentation requirements

QbD Terminology and development



TTP

Target Product Profile, is the driver

- ▶ From the TTP can define the QTTP - Quality Target Product Profile
- ▶ This will typically define the desired characteristics of the product itself
- ▶ Many related only to production

CQA

Critical to Quality Attributes

- ▶ Introduced in ICH Q8 and part of Duran's work
- ▶ Once a (Q)TPP has been established, the "Critical Quality Attributes (CQAs)" for the product can be defined
- ▶ Not all attributes are critical to the quality of the product, and so some work will need to be done in order to establish what is critical and what is not
- ▶ Can rank order of importance of the various attributes, focus on the most critical parameters and consequently de-risk the product LTFU (Lost to Follow-Up)

CTQ

Critical to Quality factors

- ▶ Introduced in GCP Renovation document (Jan '17) and in ICH E8 R1
- ▶ CTQs are the internal critical quality parameters that relate to the wants and needs of the customer.
- ▶ The (internal and external) customer requirements get translated into Critical-To-Quality (CTQ) features.
- ▶ These CTQs define the criteria to evaluate what good looks like i.e., how well the project scope and deliverables meet requirements

QTL

Quality Tolerance Limits (ICH E6 R2)

- ▶ Ability to move away from "perfection" to defined quality
- ▶ Most CTQ should have a paired QTL to measure
- ▶ Forms an essential part of Plan-Do-Study-Act cycle

QbD Terminology and development

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Customer Requirements

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Internal definition Of Critical

CTQ

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What to Measure

QTL

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Defined quality and acceptable deviations

Terminology, example

- ▶ Target Product Profile (TPP)
 - ▶ Patient wants once a day dosing
- ▶ Critical Quality Attribute (CQA)
 - ▶ Once a day dosing
- ▶ Critical to Quality factor (CTQ)
 - ▶ In early stage trials drug levels shown at 24 hours
 - ▶ In Phase 2-3 demonstrate efficacy
- ▶ Quality Tolerance Limit
 - ▶ Pre-define what will be acceptable limits for acceptance

ICH E.6 R2 section on QTL

5.0.4 Risk Control

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.

Shewhart



Deming



Statistical
Quality
Control
1930's

Total Quality
Control
1956

Statistical
Process
Control
1960's

Company
Wide Quality
Control
1968

Total Quality
Management
1985

Six Sigma
1986

Application
of statistical
methods,
control
charts and
acceptance
sampling, in
quality
control

Stress on
involving
other
departments
in addition to
production
.e.g.
Finance, HR,
etc

Inspired by
control
systems, use
of control
charts to
monitor
individual
industrial
process

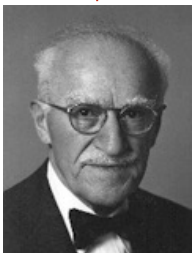
Japanese
style total
quality
control

Originating
with US
Department
of Defence

Statistical
quality
control as
applied to
business
strategy

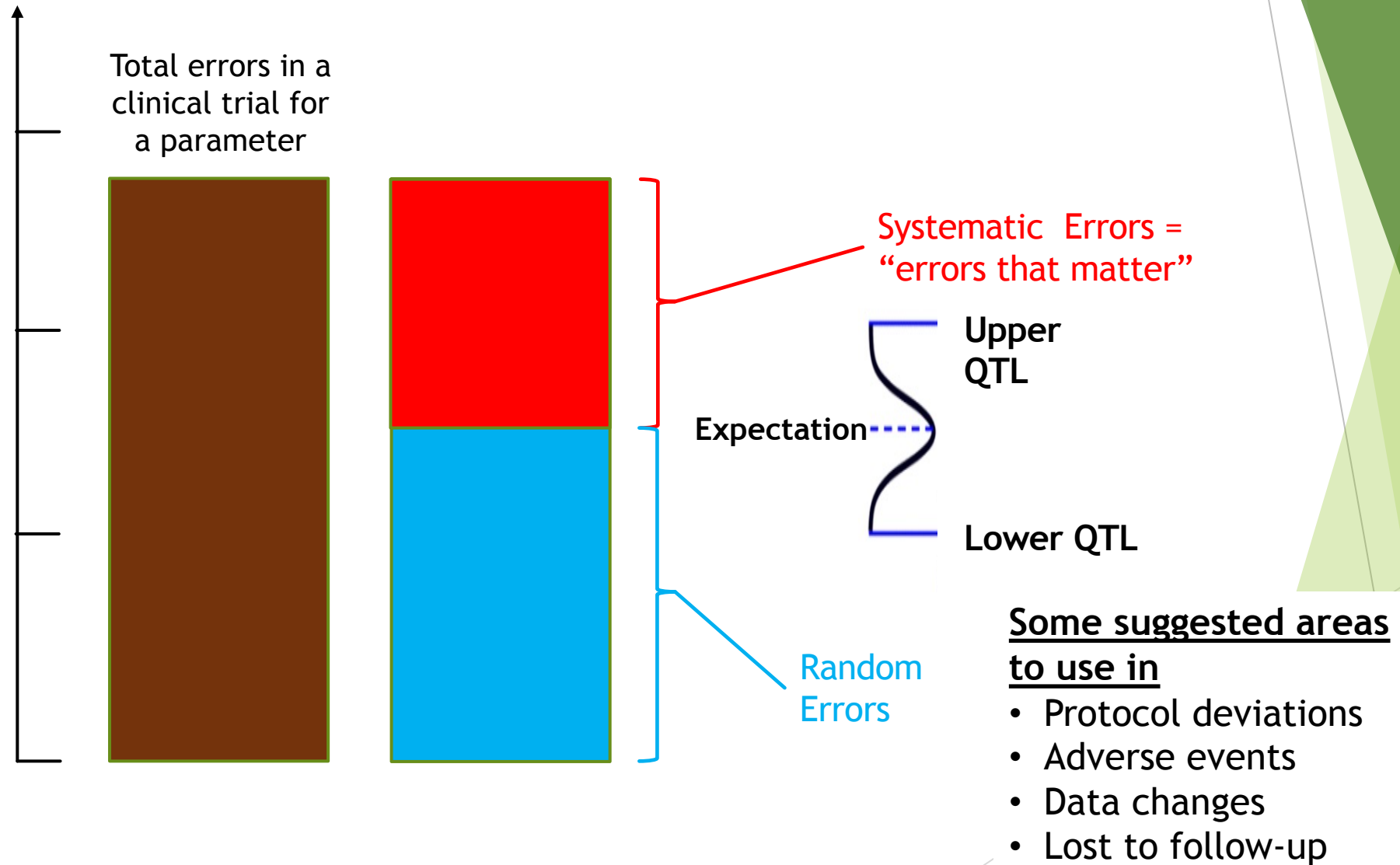
Tolerance Limits

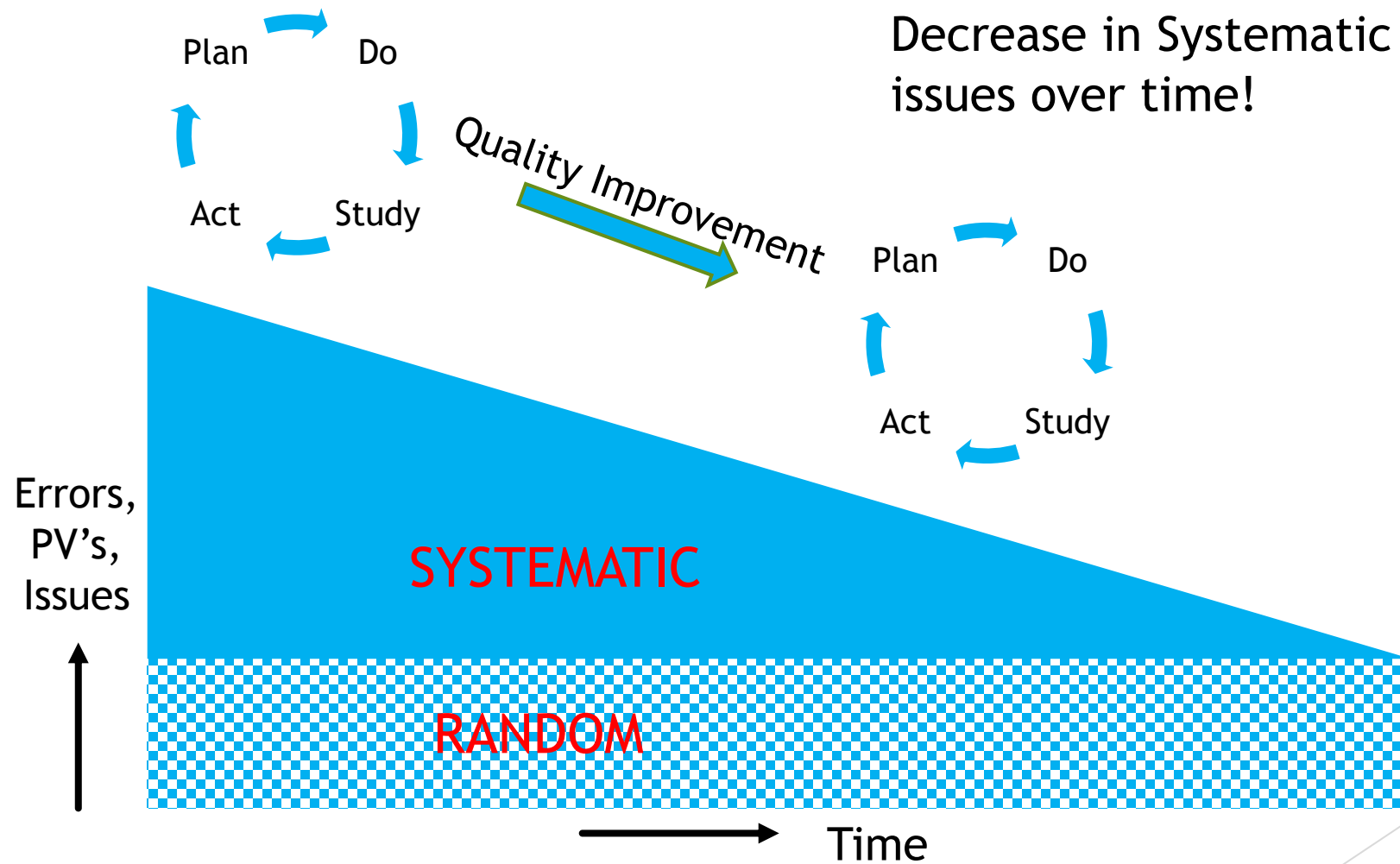
Juran



Quality by Design

Quality Tolerance Limits

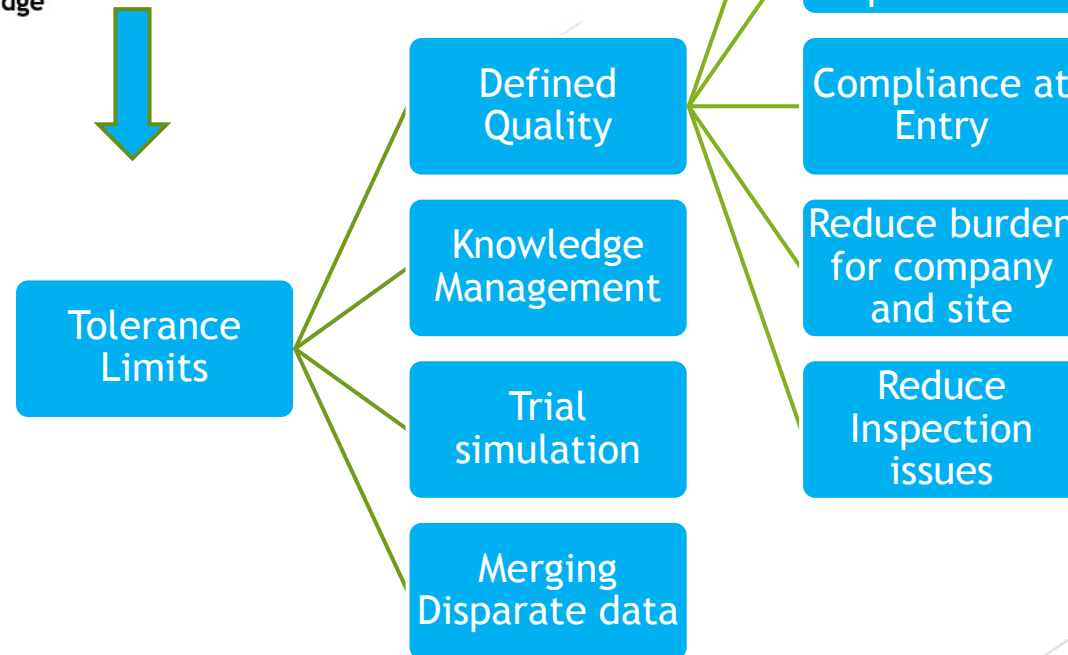
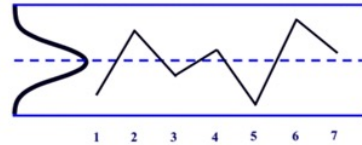
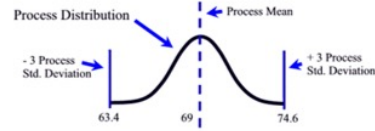




Tolerance Limits - Acceptable Defects: Rather than waste efforts on zero-defect goals, W Edwards Deming

What is a tolerance limit

- A tolerance interval can be seen as a statistical version of a probability interval
 - One sided e.g. non compliance, PV
 - Two sided e.g. AE reporting, endpoint
- Used in engineering and manufacturing
- Standard part of the quality process
- Based on standard statistical methodology
 - Action limits
 - Warning limits
 - Control mechanisms when trending out of sequence
 - CUSUM
- Needs to be defined for Clinical Trials
- Base on Statistical and Medical knowledge



Summary: What can Tolerance Limits give us

Quality by Design

Why have Sponsors not implemented QbD

- ▶ We have, it is already well established on the pharma manufacturing side
- ▶ Reasons given
 - ▶ Regulatory bodies
 - ▶ Sponsors have relied on the Randomised Clinical Trial
 - ▶ Fear of defining quality and failing
 - ▶ Too much variability between patients, sites, countries
 - ▶ Poor root cause analysis
 - ▶ Lack of understanding of QbD benefits
 - ▶ A change - why, when we are happy and have defined processes!

Summary

- ▶ Understand QTLs - They are your friend if used correctly
- ▶ Understand QbD - It can save the organisation money and improve (define) quality
- ▶ Implement holistically, not as silos

Q & A

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Confidential

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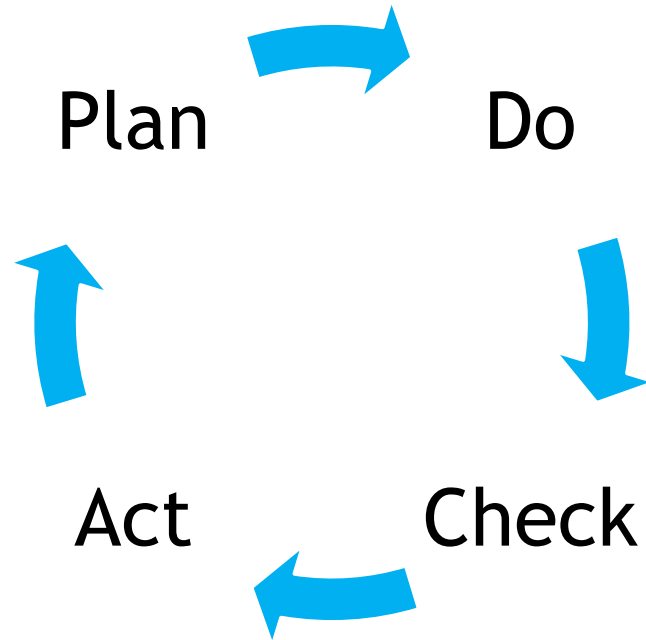
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References

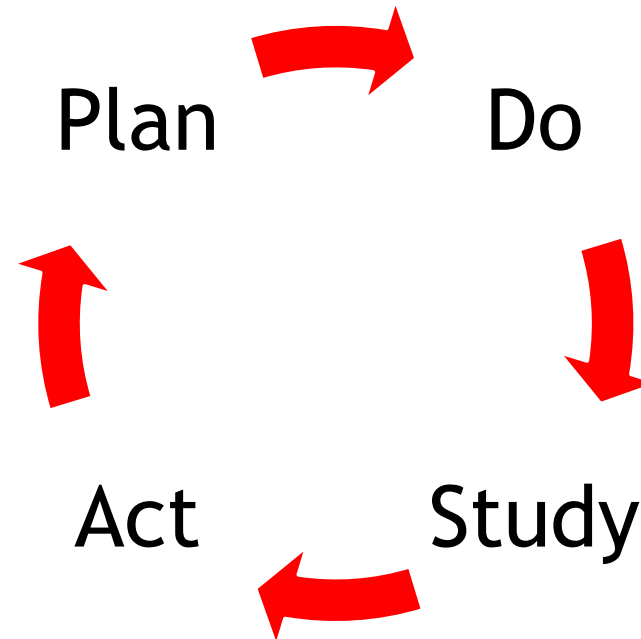
- 1982- W.E. Deming's Quality, Productivity, and Competitive Position with 14 Key Principles
#3- Cease dependence on inspection to achieve quality. Eliminate the need for massive inspection by building quality into the product in the first place.
- 1986- Motorola develops Six Sigma • 1987- FDA's first Guideline on Process Validation
- 1988- US DoD implements Total Quality Management
- 1991- J. Juran's Juran on Quality by Design: the new steps for planning quality into goods and services
- 1999- Early, J.F. and O. Coletti. Section 3: "The Quality Planning Process." Juran's Quality Handbook. 5th Ed.
- 2003- The Philosophy of Shewhart's Theory of Prediction, Mark Wilcox, Proceedings of the 9th Research Seminar: Deming Scholar's Program
- 2005- ICH QbD related drafts appear- ICH Q8-11
- 2008- FDA's Guidance for Industry Process Validation: General Principles and Practices (Rev. 1, 2011)
- 2014- Sheetz et al, Evaluating Source Data Verification as a Quality Control Measure in Clinical Trials, TIRS
- 2015- LTFU and Withdrawal of Consent in Contemporary Global Cardiovascular Randomised Clinical Trials. Rodriguez et al, Critical Pathways in Cardiology
- 2015- Knepper et al, Detecting Data Quality Issues in Clinical Trials: Current Practices and Recommendations, TIRS
- 2016- WHO : GUIDANCE ON GOOD DATA AND RECORD MANAGEMENT PRACTICES, Annex 5
- 2016- ICH : ICH E6 (GCP) Revision
- 2017- TransCelerate Risk Based Quality Management: QUALITY TOLERANCE LIMITS AND RISK REPORTING

PDCA vs PDSA



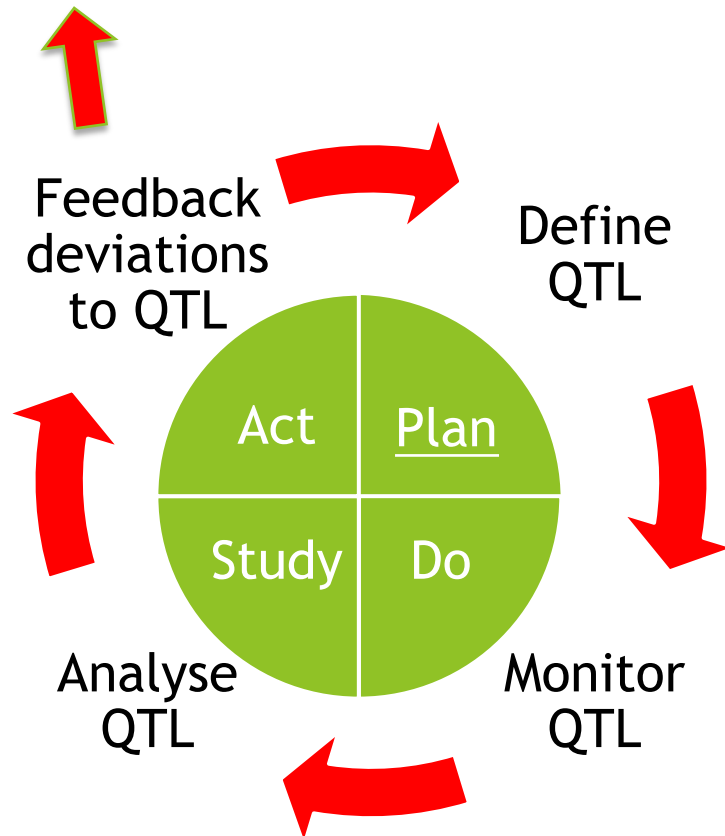
Shewhart -
Plan-Do-Check-Act

Deming –
Plan-Do-Study-Act



“Quality 101 - Deming - PDSA cycle”

Feedback into process improvement (QbD) to eliminate systematic errors



QbD Elements: Plan-Do-Study-Act

The “Plan-Do-Study-Act” framework succinctly encapsulates the key elements of QbD.

The “Plan” phase requires “design diligence.” The study design presented in the protocol must focus on proactive quality risk management and, specifically, scientific risk assessments: ensuring the safety of the study participants who will be recruited via carefully determined inclusion and exclusion criteria, the study’s scientific objectives, and the assessments and procedures that will generate the data collected. Operational plans will be created for site/country selection, quality, data monitoring, and safety. Define CQA (Critical Quality Attributes) and this should lead to selection of QTLs

In the “Do” phase of the cycle, training investigational sites, principal investigators, monitors, and clinical trial educators is the first step. Then you need to set up the process for overseeing trial execution, including prospective alerts, triggers, and risk mitigation plans that deliver against iterative project management plans.

The “Study” phase uses analytics to review the QTLs and metrics to examine the process (root cause analysis) for non random (systematic) errors.

The “Act” phase entails the final proactive (rather than reactive) step in QbD. It involves feeding the a fix for the root cause of any identified systematic errors. Reforecasting is conducted based on information gained to date and QA/quality management processes followed.