ICH E.6 (GCP) – Quality Tolerance Limits

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Topics

- Quality by Design
- Review of the of ICH E.6 Addendum on Quality Tolerance Limits
  - Overview of changes
  - Details of ICH E6 addendum text and interpretation
  - Focus on Tolerance Limits and Quality Report
  - What is the basis of this approach - W Edwards Deming's work

Quality by Design

IT IS NOT Quality control testing

Pharma currently uses

- Retrospective document checking
- Monitoring
- Auditing

To define quality, as did the British motor industry in the 1950's

ICH E8 R1

3.1 Quality by Design of Clinical Studies

"Quality should rely on good design and its execution rather than overreliance on retrospective document checking, monitoring, auditing or inspection"

Where we need to be

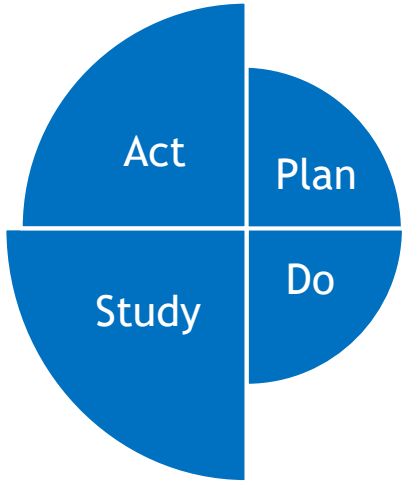
Pharma currently uses

- Reduce reliance on retrospective document checking, Monitoring and auditing
- Start to measure quality
- Predefine quality expectations

We can only work well with a vendor if we can have a measured delieverable, not a pile of documents (SOPs / plans) that describe some perfect state which is not achievable

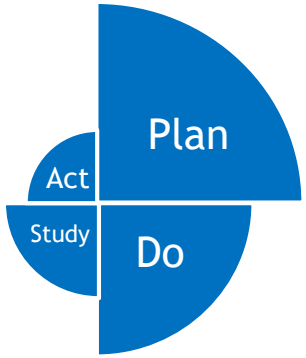
Industry Approaches to Quality

Typical Manufacturing



Amazon

Amazon pride themselves in making failures into successes, they make big gambles like Pharma but “study” the cause of failing and change their approach (“Act”).



Pharma

Pharma tend to go back to “training” or the “Plan” with failures, which results in lots of plans. The “Do” part is not undertaken to the same level. “Study” only undertaken on SAP, so no analytics on failures except individual cases. Failure to “Study” also leads to a failure to “Act” as shown by Pharma not stopping “failed” drug developments

Plans
Monitoring
Central Monitoring
Training
Communication
PV
Data Management
Statistical Analysis
etc

Drivers for ICH E.6 Addendum changes

- Concerns over quality from Regulatory Authorities
  - Lack of trust for ICH-GCP statements in submission on Audits
  - Upset over lack of transparency
    - Want defined quality
    - Transparency
  - Quality by Design, not chance
  - Quality throughout the organisation – not as isolated islands
  - Lack of oversight
  - Poor “Root cause analysis”
  - Pharma is wasting resources – greater efficiency leads to
    - More new drug
    - Reduced costs

ICH E6 addendum

5.0.4 Risk Control

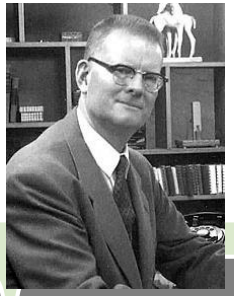
Predefined quality tolerance limits should be established, taking into consideration the **medical and statistical** characteristics of the variables as well as the statistical design of the trial, to **identify systematic issues** that can impact subject safety or reliability of trial results. Detection of deviations from the predefined quality tolerance limits should **trigger an evaluation** to determine if action is needed.

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** in the clinical study report (ICH E3, Section 9.6 Data Quality Assurance)

Shewhart

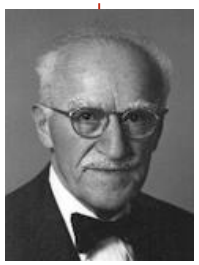
Deming



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 → ICH E6 R2

Juran



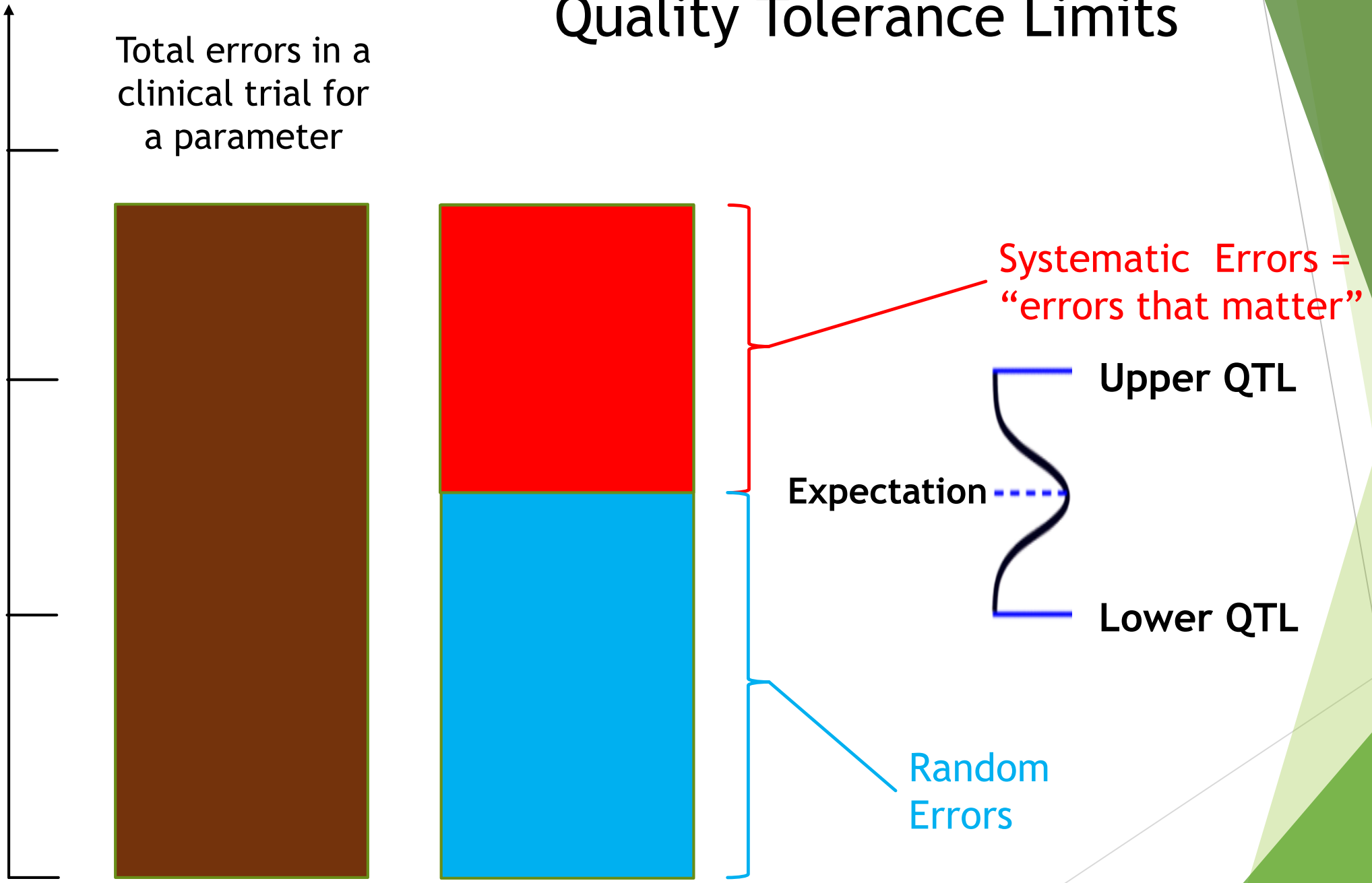
Quality by Design → ICH E8 R1

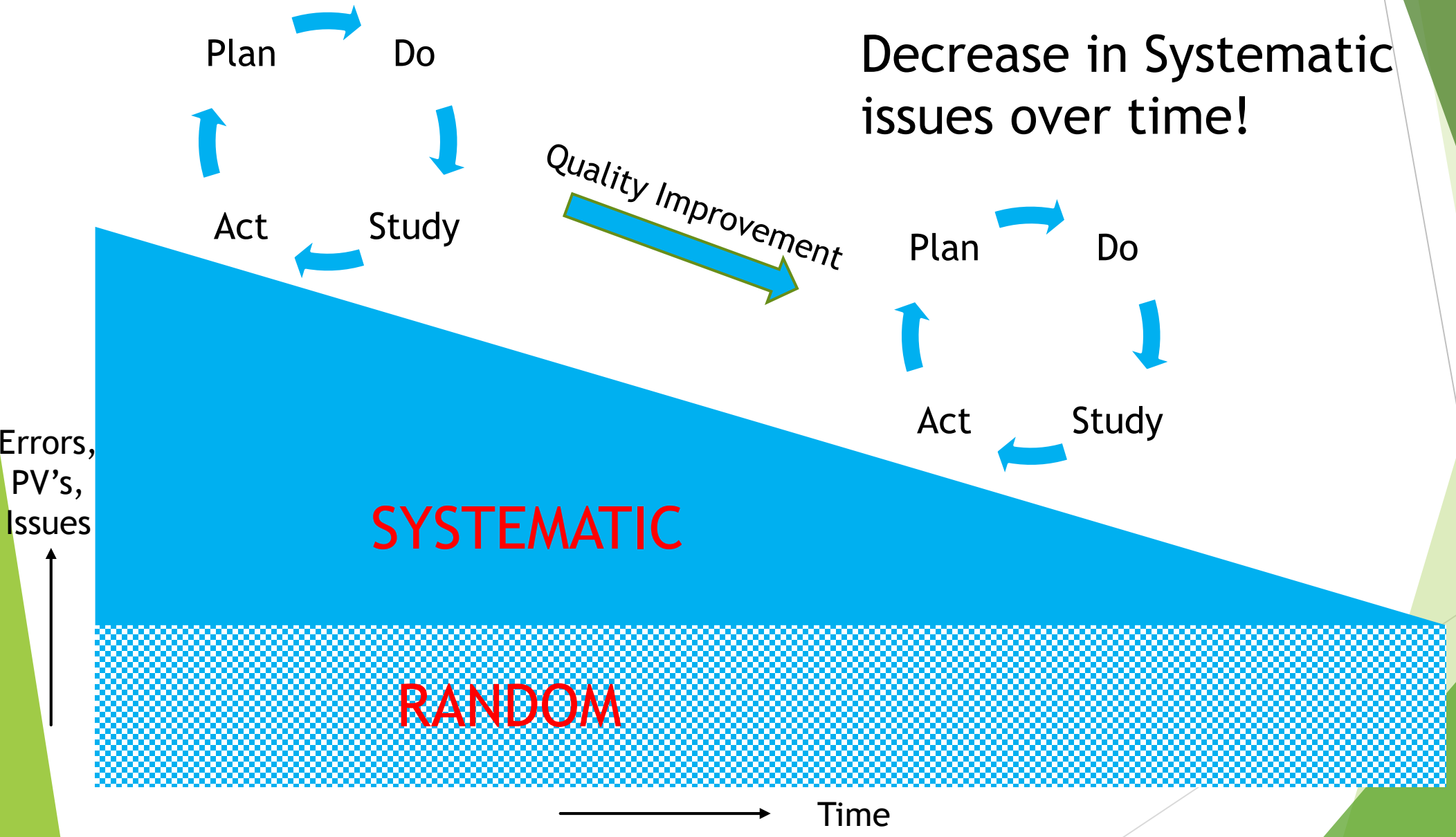
Acceptable Defects: Rather than waste efforts on zero-defect goals, W Edwards Deming

Areas to be addressed

- What is a tolerance limit, how should it be used
- Non Compliances and Important Protocol Violations
  - Need methodology
- Primary endpoint
  - Company specific determination
  - Examples can be given
- Missed Adverse Events
  - Use basic research from publications
- General Error rate
  - Develop methods based on TransCelerate SDV paper

Quality Tolerance Limits





Decrease in Systematic issues over time!

How to calculate the expected number

Historical (Internal)

- Use trials from previous work in the project
  - Need to define what may be systematic issue in a site e.g. more than 2 PV/PDs of the same type

Historical (external)

- Use data from publications e.g.

LTFU (Lost to Follow-Up)

Paper from Stanford –" Lost to Follow-up and Withdrawal of Consent in Contemporary Global Cardiovascular Randomized Clinical Trials." Rodriguez at al, Critical Pathways in Cardiology 2015

SDV & Monitoring

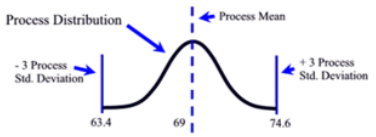
Evaluating Source Data Verification as a Quality Control Measure in Clinical Trials", Sheetz et al, TIRS 2014

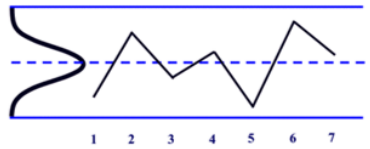
Profound Knowledge

- Knowledge of the process, converted to metrics of
  - Clinical Trials
  - Protocol
  - Indication
  - Sites
  - Size of sites
  - Countries being used
  - Company

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

Q & A

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