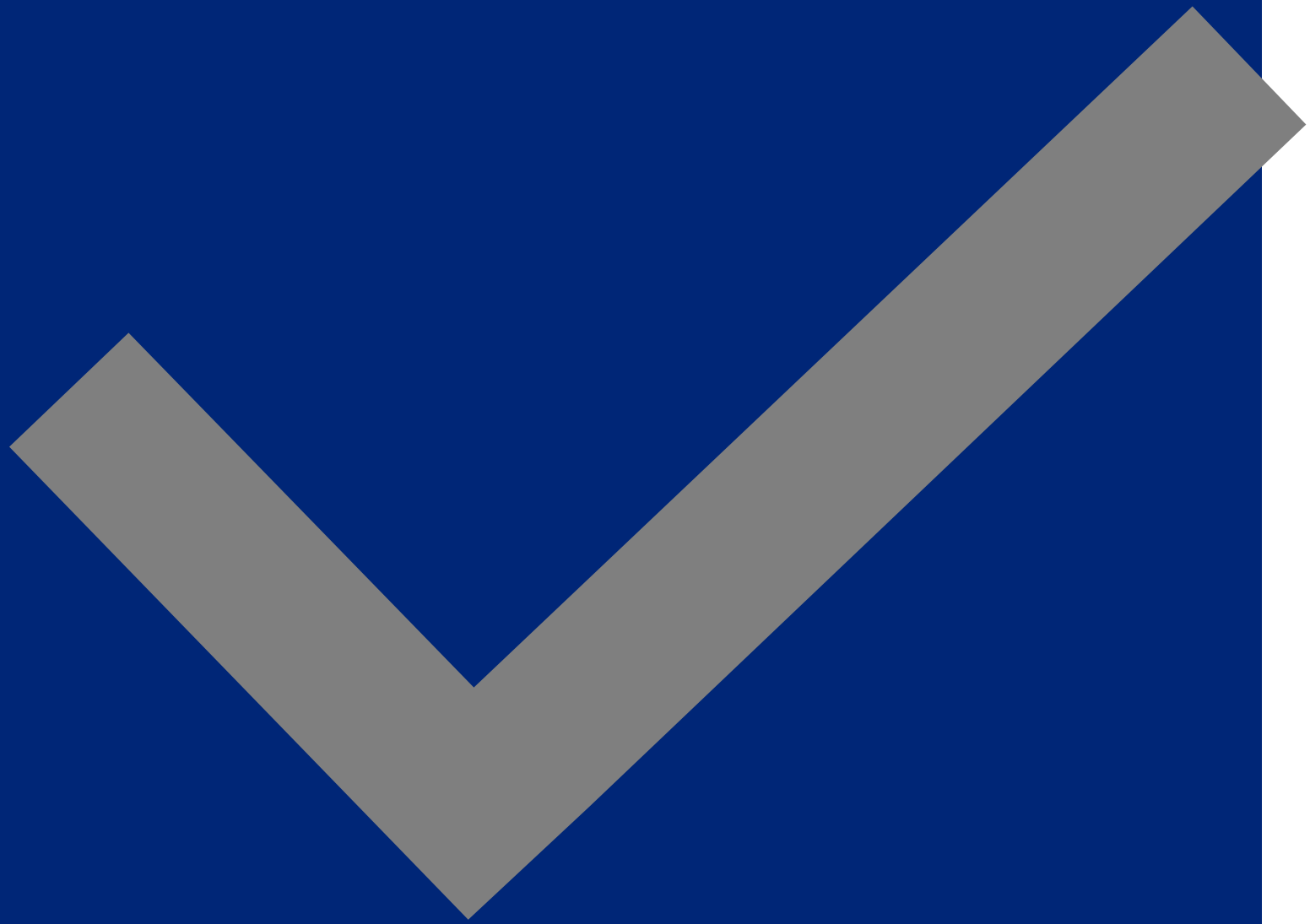
The Fundamentals of QCing

Paul Vervuren

PSDM Networking Event

November 26th, 2024



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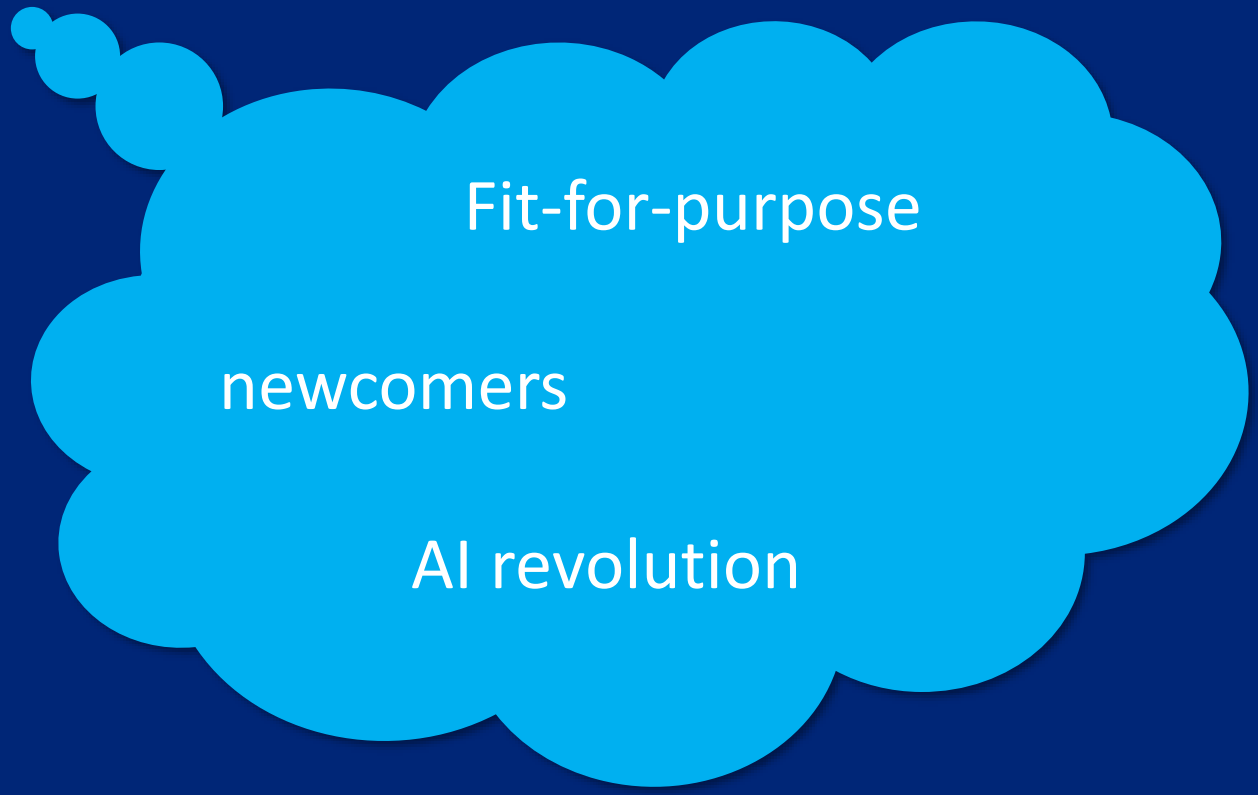

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Agenda

- Quality, What and Why
- ICH Guidelines:
  - Explore requirements for Stat Programming
  - Definitions (QC/QA, QC/Validation)
  - What's new in ICH E6(R3), draft guideline
- Programming 'Operational Practice'
- Success factors for streamlining QC
- Summary
- Q&A / Discussion

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#3796248

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Definition of Quality

According to ISO and ICH

Quality is the “degree to which a set of inherent characteristics [or distinguishing features] of an object”, which in turn is defined as anything perceivable or conceivable, such as a product, service, process, person, organization, system or resource, “fulfils requirements.”

ISO International Organization for Standardization

ICH harmonisation for better health

Quality: The degree to which a set of inherent properties of a product, system or process fulfills requirement

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To whom does quality matter?

in the context of clinical studies

- Participants
- Investigators
- Regulators
- Sponsors

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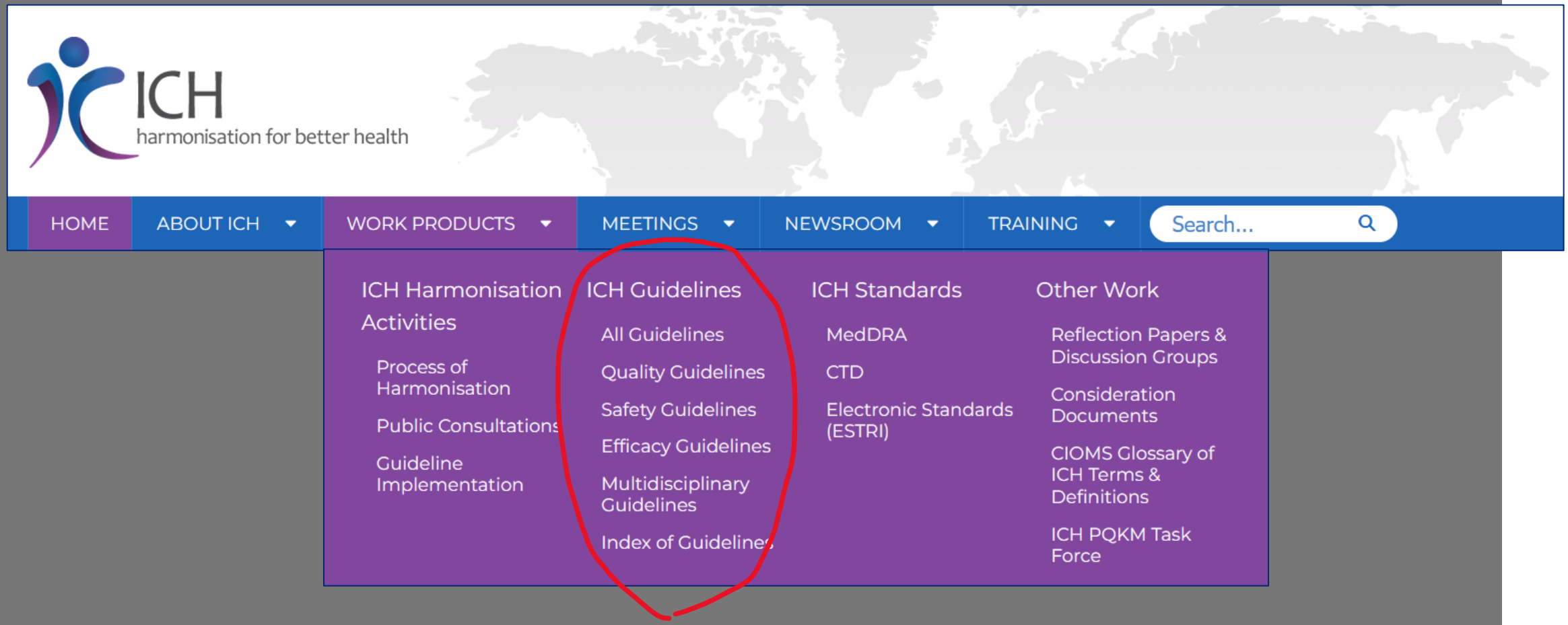
The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use



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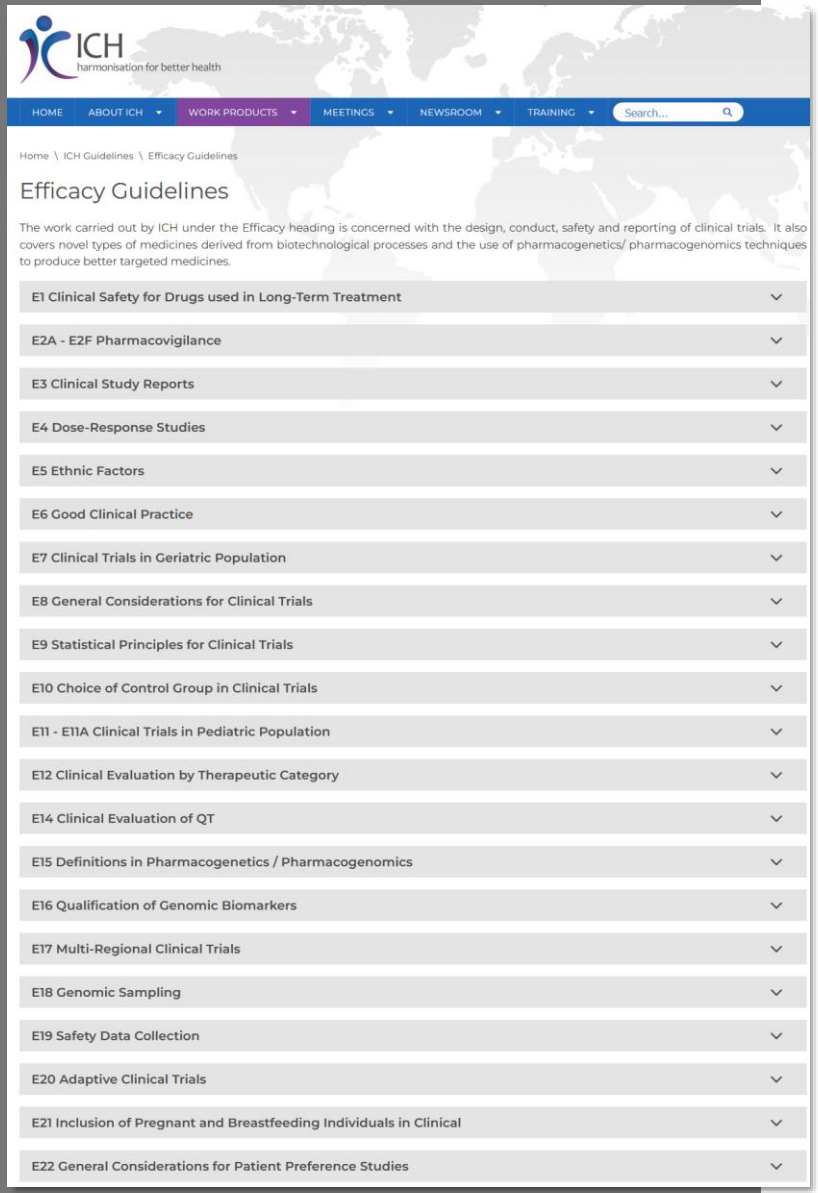
Which are the most relevant ICH Guidelines for Quality Control in Statistical Programming

Most relevant ICH guidelines for QC in Statistical Programming

- E6 Good Clinical Practice
- E9 Statistical Principles for Clinical Trials
- E8 General Considerations for Clinical Studies
- E3 Clinical Study Reports



The Efficacy Guidelines are concerned with the design, conduct, safety and reporting of clinical trials

www.ich.org/page/efficacy-guidelines

Releases of the ICH Efficacy Guidelines

• 1996	E6(R1) Good Clinical Practice	R2, 2016	R3 draft, 2023
• 1997	E8 General Considerations for Clinical Studies	R1, 2021	
• 1998	E9 Statistical Principles for Clinical Trials	R1 Addendum, 2019	

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Releases of the ICH Efficacy Guidelines

advancements in technology and risk management

• 1996	E6(R1) Good Clinical Practice	R2, 2016	R3 draft, 2023
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‘Addendum on estimands and sensitivity analysis in Clinical Trials’

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"quality by design" approaches and wider range of study designs and data sources

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Releases of the ICH Efficacy Guidelines

- Encourage fit-for-purpose approaches
- Improve clarity and readability
- Provide practical and feasible expectations for responsibilities
- And more …

• 1996 E6(R1) Good Clinical Practice	R2, 2016	→ R3 draft, 2023
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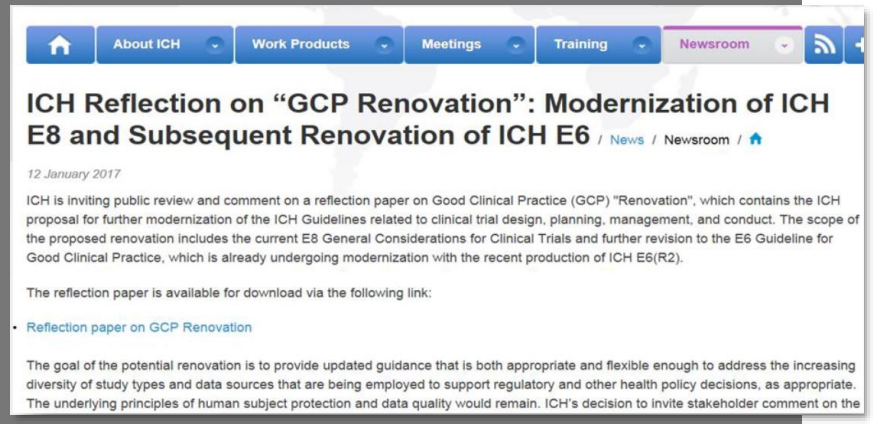

https://admin.ich.org/sites/default/files/2021-05/ICH_ReflectionPaper_GCPRenovation_2021_0519.pdf

Which are the two new principles in ICH E6(R3)?

ICH E6 (R3) PRINCIPLES

ICH E6 (R3) PRINCIPLE	TOPIC	ICH E6 (R2) REF
1	Ethical Principles	2.1, 2.2, 2.3, 2.7, 2.11
2	Informed Consent	2.9
3	IRB/IEC Review	2.6
4	Science	2.4, 2.5
5	Qualified Individuals	2.8
6	Quality	2.13
7	Risk Proportionality	N/A
8	Protocol	2.5
9	Reliable Results	2.10
10	Roles and Responsibilities	N/A
11	Investigational Products	2.12

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5	Qualified Individuals	2.8
6	Quality	2.13
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9	Reliable Results	2.10
10	Roles and Responsibilities	N/A
11	Investigational Products	2.12

ICH E6(R2) Good Clinical Practice

GCP principles most relevant to QC in Statistical Programming

- All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification. (2.10)

We need to take proper care of data from start to end.

Analysis results must be accurate and verifiable

- Systems with procedures that assure the quality of every aspect of the trial should be implemented. Aspects of the trial that are essential to ensure human subject protection and reliability of trial results should be the focus of such systems. (2.13)

We need to have adequate systems and procedures

The GCP principles are intended to ensure ethical trial conduct and reliable results

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What is the difference between QC and QA?

Quality Control & Quality Assurance

ICH E6(R2) Glossary

- Quality Control (QC): The operational techniques and activities [..] to verify that the requirements for quality of the trial-related activities have been fulfilled.

- Quality Assurance (QA): All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirement(s).

QC

Checking

QA

Ensuring process compliance

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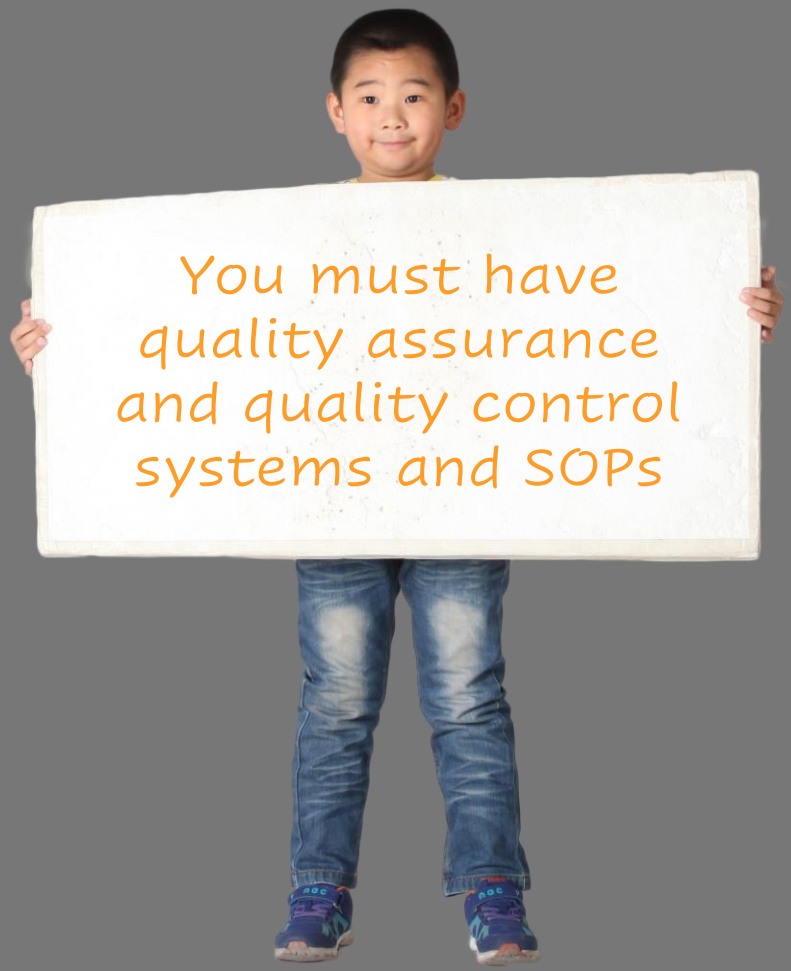
E6(R2) Section 5. Sponsor responsibilities

5.1 Quality Assurance and Quality Control

- The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s).

- Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.



Note: the sponsor may use a CRO, but remains ultimately responsible for the quality and integrity of the trial data (section 5.2.1)

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What do the current Efficacy guidelines say about program validation?

Quality Control vs. Validation

E9 Statistical Principles for Clinical Trials

Section 5.8 Integrity of Data and Computer Software Validity

The credibility of the numerical results of the analysis depends on the quality and validity of the methods and software (both internally and externally written) used both for data management (data entry, storage, verification, correction and retrieval) and also for processing the data statistically. [...].

The computer software used for data management and statistical analysis should be reliable, and documentation of appropriate software testing procedures should be available.

Software for statistical analysis must be reliable and appropriately tested (validation)

Quality Control vs. Validation – continued

E6(R2) Good Clinical Practice

Section 5.5 Trial Management, Data Handling, and Record Keeping

5.5.3. When using electronic trial data handling and/or remote electronic trial data systems, the sponsor should:

(a) Ensure and document that the **electronic data processing system(s)** conforms to the sponsor's established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e., validation).

The sponsor should base their approach to **validation of such systems** on a risk assessment that takes into consideration the intended use of the system and the potential of the system to affect human subject protection and reliability of trial results.

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Requirements for data processing and statistical analysis

Focussing on Statistical Programming

E6(R2) 5.5.4.

If data are transformed during processing, **it should always be possible to compare the original data and observations with the processed data**.

Traceability, lineage

E9 5.8 **Integrity of Data** and Computer Software Validity

The credibility of the numerical results of the analysis depends on the quality and validity of the methods and software (both internally and externally written) used both for data management (data entry, storage, verification, correction and retrieval) and also for processing the data statistically. Data management activities should therefore be based on thorough and effective standard operating procedures.

Need valid methods for processing the data to produce credible analysis results

Requirements for data processing and statistical analysis

Focussing on Statistical Programming

E9 7.1 Evaluation and Reporting

As stated in the Introduction, the structure and content of clinical study reports is the subject of ICH E3. That ICH guidance fully covers the reporting of statistical work, appropriately integrated with clinical and other material. The current section is therefore relatively brief.

During the planning phase of a trial the principal features of the analysis should have been specified in the protocol as described in Section 5. When the conduct of the trial is over and the data are assembled and available for preliminary inspection, it is valuable to carry out the blind review of the planned analysis also described in Section 5. This pre-analysis review, blinded to treatment, should cover decisions concerning, for example, the exclusion of subjects or data from the analysis sets; possible transformations may also be checked, and outliers defined; important covariates identified in other recent research may be added to the model; the use of parametric or non-parametric methods may be reconsidered. Decisions made at this time should be described in the report, and should be distinguished from those made after the statistician has had access to the treatment codes, as blind decisions will generally introduce less potential for bias. Statisticians or other staff involved in unblinded interim analysis should not participate in the blind review or in making modifications to the statistical analysis plan. When the blinding is compromised by the possibility that treatment induced effects may be apparent in the data, special care will be needed for the blind review.

Many of the more detailed aspects of presentation and tabulation should be finalised at or about the time of the blind review so that by the time of the actual analysis full plans exist for all its aspects including subject selection, data selection and modification, data summary and tabulation, estimation and hypothesis testing. Once data validation is complete, the analysis should proceed according to the pre-defined plans; the more these plans are adhered to, the greater the credibility of the results. Particular attention should be paid to any differences between the planned analysis and the actual analysis as described in the protocol, protocol amendments or the updated statistical analysis plan based on a blind review of data. A careful explanation should be provided for deviations from the planned analysis.

All subjects who entered the trial should be accounted for in the report, whether or not they are included in the analysis. All reasons for exclusion from analysis should be documented; for any subject included in the full analysis set but not in the per protocol set, the reasons for exclusion from the latter should also be documented. Similarly, for all subjects included in an analysis set, the measurements of all important variables should be accounted for at all relevant time-points.

The effect of all losses of subjects or data, withdrawals from treatment and major protocol violations on the main analyses of the primary variable(s) should be considered carefully. Subjects lost to follow up, withdrawn from treatment, or with a severe protocol violation should be identified, and a descriptive analysis of them provided, including the reasons for their loss and its relationship to treatment and outcome.

limit bias and ensure credibility of the analysis:
- blinded review
- pre-specification of the statistical analysis plan

Need to account for exclusion/assignment of subjects

Requirements for data processing and statistical analysis

Focussing on Statistical Programming

E8(R1) General Considerations for Clinical Studies

5. DESIGN ELEMENTS AND DATA SOURCES FOR CLINICAL STUDIES

5.7. Study Data

- Study data should be of sufficient quality to address the objectives of the study and, in interventional studies, to monitor participant safety. **Data quality attributes include consistency (uniformity of ascertainment over time), accuracy (correctness of collection, transmission, and processing), and completeness (lack of missing information)**.
- The use of standards for data recording and coding (or recoding) is important to support data reliability, facilitate correct analysis and interpretation of results, and promote data sharing. **Internationally accepted data standards exist for many sources of study data and should be used where applicable**.

Defines data quality attributes:
consistency, accuracy and completeness

Promotes the use of data standards
('should be used where applicable')

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What have we learned so far

- Systems and procedures for QC and QA
- Compliance with the protocol and applicable regulation
- Taking care of data throughout the life cycle
- Sufficient data quality (consistency, accuracy and completeness)
- Traceability
- Use of industry data standards
- Credibility of analysis (methods, blinding)
- Account for exclusion of subjects and data points

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More clarity and coherence in E6(R3)

Draft version 19 May 2023. Currently under public consultation

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3. SPONSOR

3.16 Data and Records

3.16.1 Data Handling

3.16.2 Statistical Programming and Data Analysis

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elaborates on data collection, data management, changes to data, access, systems, confidentiality, privacy protection, blinding, … (23 points)

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3.16.2 Statistical Programming and Data Analysis

- Documented quality control of statistical programming and data analysis
- Traceability of data transformations and derivations
- Documentation of inclusion or exclusion of participants or data points
- Retain statistical programming records including quality control activities performed
- Outputs should be: traceable to the programs, time-stamped, protected against changes

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4. DATA GOVERNANCE – INVESTIGATOR AND SPONSOR

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More clarity and coherence in E6(R3)

Draft version 19 May 2023. Currently under public consultation

3. SPONSOR

3.16 Data and Records

Responsibilities & requirements

3.16.1 Data Handling

elaborates on data collection, data management, changes to data, access, systems, confidentiality, privacy protection, blinding, … (23 points)

3.16.2 Statistical Programming and Data Analysis

Guidance

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4. DATA GOVERNANCE – INVESTIGATOR AND SPONSOR

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Requirements for data processing and statistical analysis

Focussing on Statistical Programming

E8(R1) General Considerations for Clinical Studies

3. DESIGNING QUALITY INTO CLINICAL STUDIES

- Quality by Design
- Establishing a Culture that Supports Open Dialogue
- Reviewing Critical to Quality Factors
  - Importance of ‘accumulated experience and knowledge’ for adjusting risk control mechanisms
- Critical to Quality Factors in Operational Practice
  - “The foundation of a successful study is a protocol that is both scientifically sound and operationally feasible“

- Quality by Design
- Quality Culture
- Applying lessons learned
- Operational feasibility

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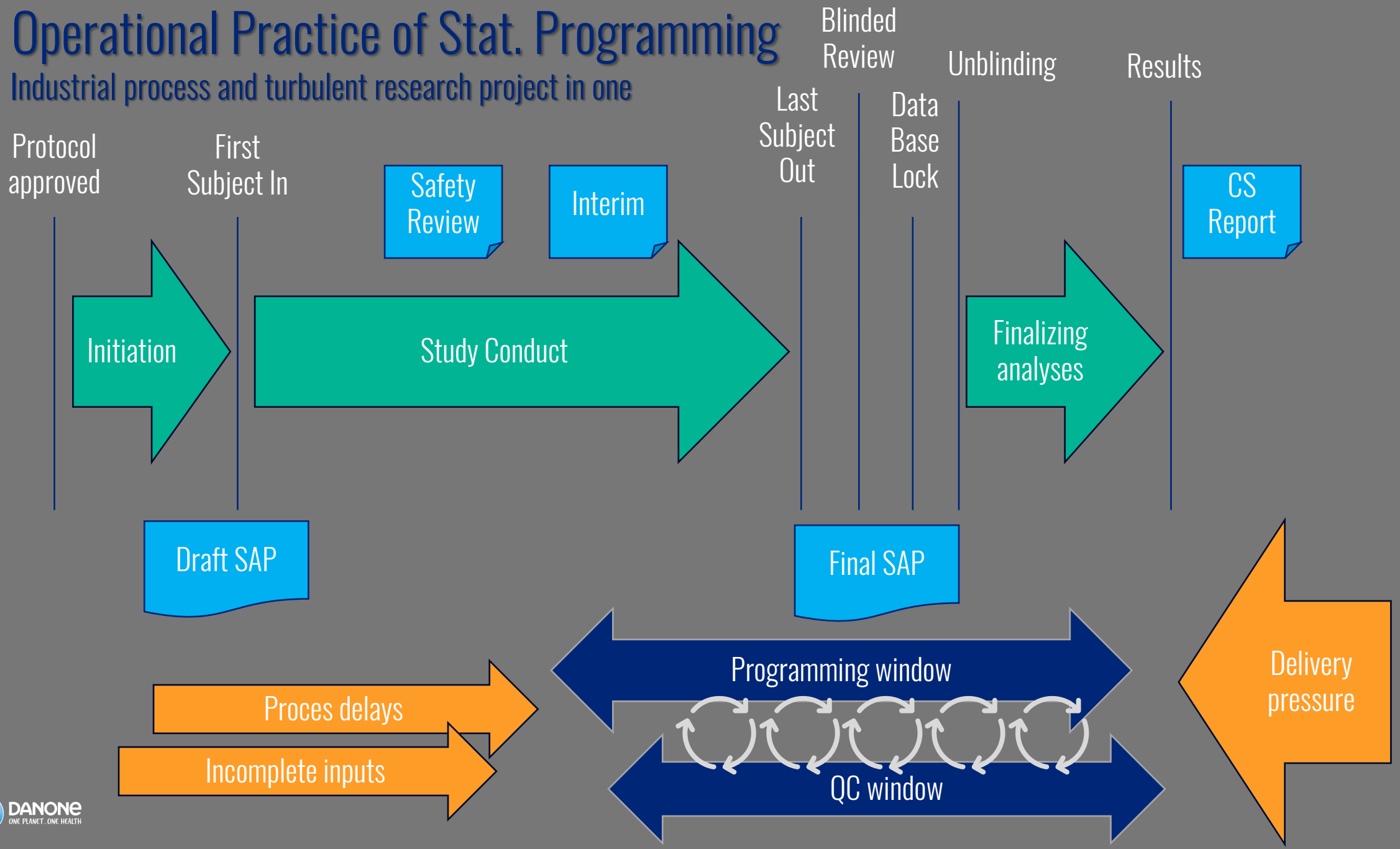
Operational Practice of Stat. Programming

Industrial process and turbulent research project in one



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Operational Practice of Stat. Programming

Volume and variety of deliverables

CS Report

Blinded Safety review

Blinded Data Review

Blinded Data Review, Interim

Interim analysis

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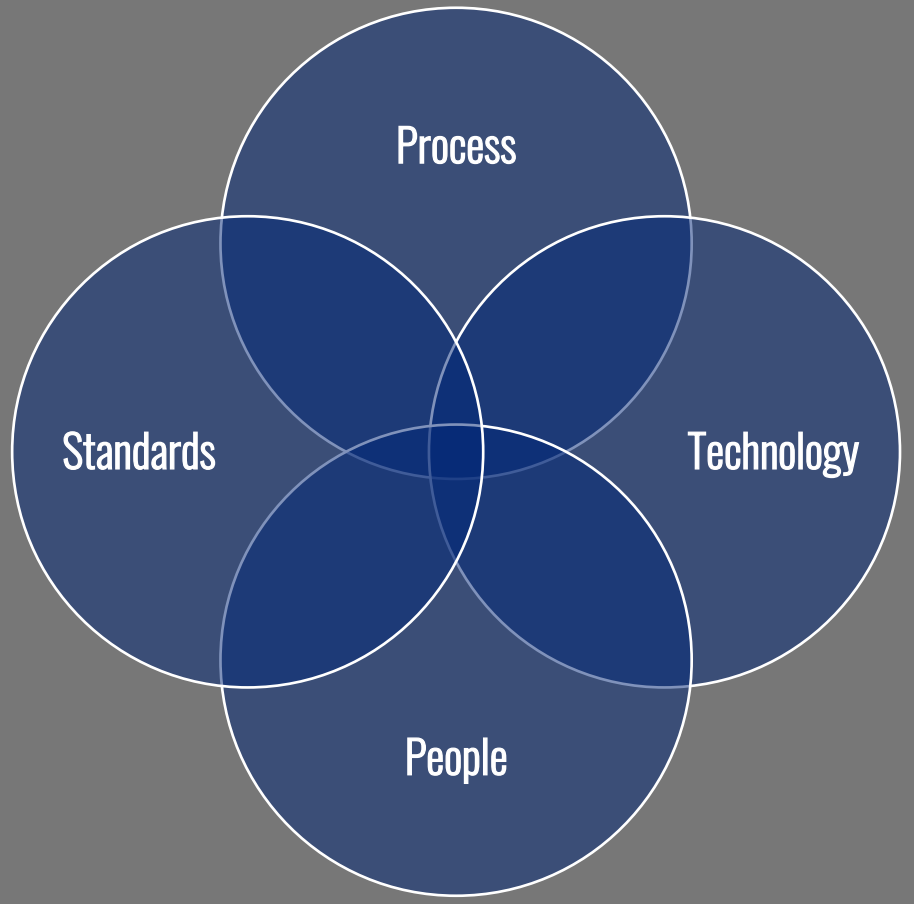
Success factors for streamlining Stat Programming QC

- Risk-based approach, Lean processes
- Standards and best practices
- Systems & Automation
- Planning and resource assignment
- Collaboration and communication
- Culture



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Summary

- ICH Efficacy guidelines: high-level requirements, clarifications in E6(R3)
- Opportunities to simplify and lower the burden of QC and QA processes
- Operational practice: dynamic, demanding, complex
- Successful QC: People (and Culture), Process, Technology and Standards