

Establishing the Context: A Review of the Principles Document

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Origins of the document

General principles about what really matters in clinical trials can and should be developed—i.e., what do we really need to get right to ensure reliability of results and patient protection?



Underlying assumption

The likelihood of a successful, quality trial can be dramatically improved through prospective attention to preventing important errors that could undermine the ability to obtain meaningful information from a trial.

Project objectives

- Produce a draft document outlining:
 - High-level principles for building quality into trials
 - One potential approach to prospective quality planning
- Test and refine the document through a series of workshops
 - Different therapeutic areas
 - Different product types
 - Various stakeholders
 - Different functional lines

The wisdom of the crowd

“The process of building quality into the study plan may be informed not only by cross-functional teams at the sponsor organization, but also by participation of clinical investigators, study coordinators and other site staff, patients, and other parties to whom study-related activities will be assigned.”

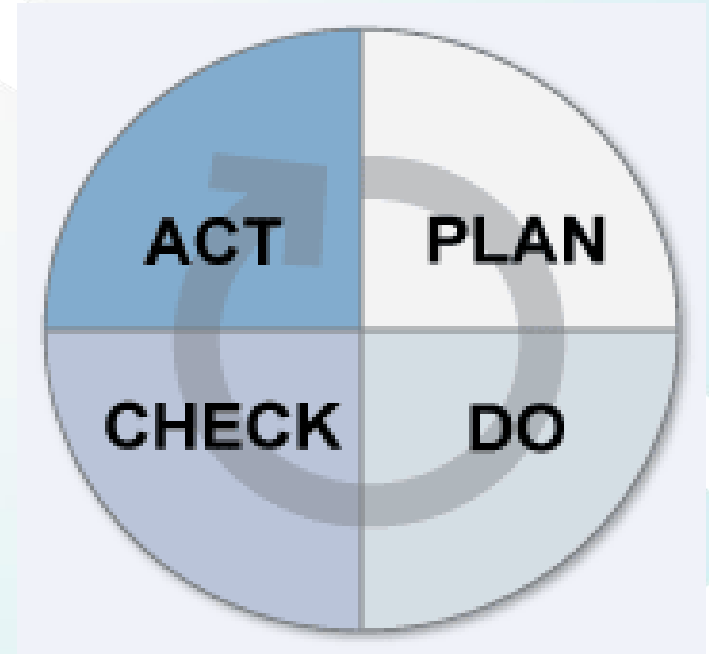
Project objectives

- In using the document, identify what worked and more importantly, what didn't
 - Process
 - Missing elements
 - Unnecessary elements
- Refine the document /approach
- Disseminate the initial results
- Encourage further development



The larger context of quality management

- Plan
 - Identify quality objectives, risks to quality, and appropriate metrics
 - Develop quality management plans
- Do – Study conduct
- Check – Measure/monitor
- Act – Respond to deviation



Key concepts

Quality in clinical trials = the absence of errors that matter



What are “errors that matter”?

- Errors that have a meaningful impact on
 - Patient safety or
 - Credibility of the results

Example: An error that mattered

- eCRF design flaws → erroneous data collection
 - Signs/symptoms for secondary endpoint
 - Screen design confused sites
 - (5) Resolved
 - (4) Worse
 - (3) Improved
 - (2) Same
 - (1) New
 - Widespread discrepancies in data entry
 - Audit trails incomplete

Key concepts: Critical to quality

Factors that are generally relevant to the integrity and reliability of conclusions based on study data and to subject safety



Principles document:

A tool for inquiry in CTQs and associated risks

Principles Document V1.0 (Sept 2012)

- Identified CTQ Factors
- Grouped Factors into 7 categories
- Developed series of “examples for consideration” for each CTQ Factor

Principles Document V2.0 (Jan 2013)

For each CTQ Factor, split “examples for consideration” into two categories:

- Potential Considerations in Evaluating Relative Importance of CTQ Factor
- Examples of Issues to Consider in Evaluating Risks to CTQ Factor

Principles document:

A tool for inquiry in CTQs and associated risks

Principles Document: Version 3 (January 2014)

- Retains the structure of Version 2
- Includes device development focused inquiry
- Expands focus of questions to more explicitly consider perspectives of stakeholders
 - Patients
 - Investigators
 - Payers
- Directly incorporates EMA reflection paper and FDA guidance on risk-based oversight more directly

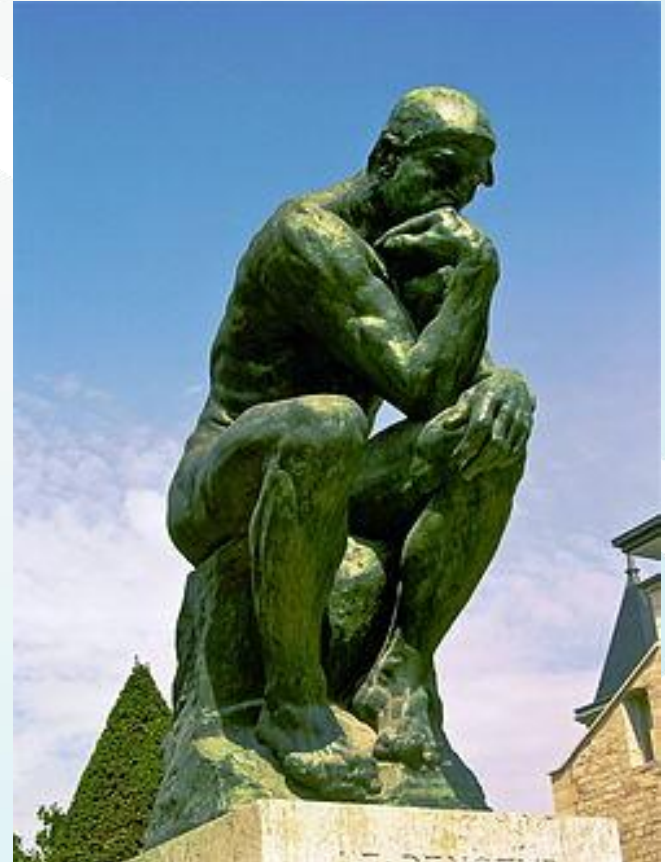
Closing thoughts: January 2013

“Many ideas grow better when transplanted into another mind than the one where they sprang up.”

- *Oliver Wendell Holmes*

Principles document intent

- Questions to promote
 - Proactive, cross-functional discussions
 - Critical thinking at the time of trial development
 - About what is critical to quality for a specific trial
 - About the events that might impede or facilitate achieving quality

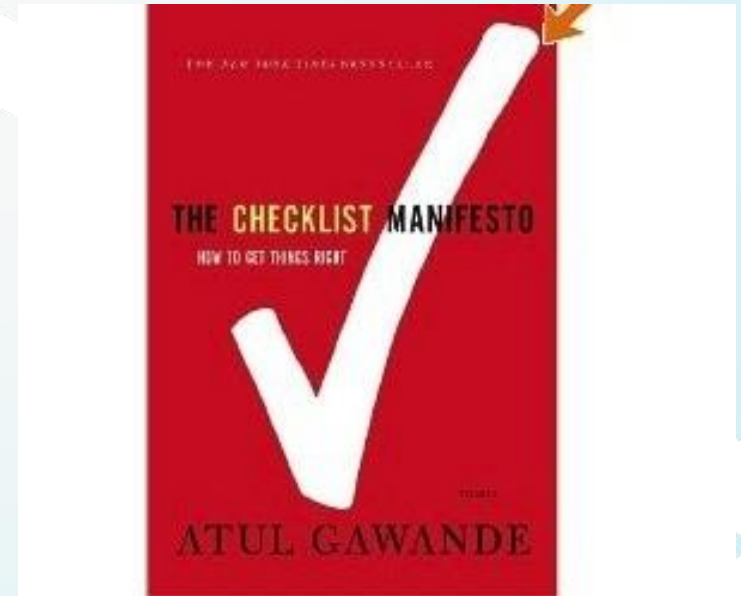


What the document isn't

- Not intended to serve as:
 - A “tick the box” exercise
 - A “checklist” to be completed in isolation
 - A substitute for experience and critical thinking
 - A quantitative risk assessment methodology
- Not all-inclusive
- Not even best practice if it were a checklist...

If you must call it a checklist...

- “A set of checks to ensure the ... critical stuff is not overlooked”
- “Another set of checks to ensure people talk and coordinate and accept responsibility while nonetheless being left with the power to manage the nuances and unpredictabilities...”



CTQs: Feasibility

- Study and Site Feasibility
- Accrual

Example: Feasibility

- Exercise may help:
 - Facilitate site selection based on “critical to quality” site attributes for the trial
 - Identify modifications in trial design
 - Identify specific topics for focused protocol training

Example: Study and Site Feasibility

Relative Importance

- Where is the trial to be conducted? Why?
- What is the standard of care in those countries/regions?
- Are there established research networks for the therapeutic area?

Risks

- Varying standards of care vs. protocol?
- Access to data on subjects lost-to-follow-up or on long-term survival?
- Skill-level / experience of non research staff in interacting with the subject? Might there be an impact on outcomes

CTQs: Protocol Design

- Endpoints
- Eligibility criteria
- Data Quantity
- Procedures supporting study endpoints and data integrity
- Type of Control
- Randomization
- Blinding
- Investigational product handling and administration

Example: Endpoints

Relative Importance

- Describe the characteristics of the primary endpoint, e.g.
 - How and by whom will it be ascertained (CI, centrally, third party uninvolved in the study)
 - Is the endpoint objective or subjective?
 - Are standardized and generally accepted endpoint definitions and methods to ascertain endpoints available?
- Have patient-reported outcomes been considered as an endpoint?

Potential Risks

- Does the primary endpoint address the study aims? Is it accepted by patients, regulators, payers, and clinicians?
- If it is a soft endpoint, is there the potential for bias to be introduced? How and by whom? How could this bias be minimized?

Example: Eligibility Criteria

Relative Importance

- Describe the specific population needed for the trial to evaluate the intended question. If this specific population is not enrolled, what's the impact?
- Evaluate the impact of “getting it wrong” with regard to eligibility? Would the subject be removed? Replaced? Counted as a treatment failure?
- Is the trial intended to evaluate effectiveness and safety of the investigational product (IP) in a real-world population?

Potential Risks

- Are all criteria relevant to ensuring the specific subject population needed for the trial?
- Are there clear and measureable criteria to define the population
- Is there a particular criterion critical to subject evaluability (e.g. for an enrichment design) or to subject safety?

CTQ: Patient Safety

- Informed Consent
- Withdrawal criteria and subject retention
- Signal detection and safety reporting
- DMC/ stopping rules (if applicable)

Example: Withdrawal Criteria / Subject Retention

Relative Importance

- Describe the situations in which subjects should or may be withdrawn from study treatment.
- For participants who stop the assigned treatment, what data are critical for study analysis and reporting?
- For this study, what steps are required prior to deeming a subject “lost to follow-up?”
- How will subjects with permanent device implants be followed upon withdrawal?

Potential Risks

- Do the withdrawal criteria capture all important and likely scenarios in which a subject should be removed?
- Are the withdrawal criteria described consistently throughout the study documents?
- How will the team ensure that withdrawal criteria are applied appropriately and consistently?
- Do subjects have personal issues that can be mitigated to aid retention?

CTQs: Study Conduct

- Training
- Data recording and reporting
- Data monitoring and management
- Statistical analysis

CTQs: Potpourri

- Study reporting
- Third party service providers

Example: Data Monitoring & Management

Relative Importance

- Define critical data elements for data management during protocol development. (Are there data not critical for study analyses)
- Identify departures from study conduct that may generate “errors that matter”
- Evaluate what type of issues the monitoring plan is designed to detect
- Evaluate use of centralized statistical monitoring in combination with other monitoring activities

Potential Risks

- Does the investigational plan clearly define which departures are “errors that matter?”
- Are planned data edit checks focused on critical data and processes?
- Have realistic tolerance limits for “errors” been defined?
- What types of discrepancies are permitted to remain through study closure?

Closing thoughts

“We are all plagued by failures – by missed subtleties, by overlooked knowledge, and outright errors. For the most part, we imagined that little could be done beyond working harder and harder to catch the problems and clean up after them...

When we look closely, we realize the same balls are being dropped over and over, even by those of great determination. **We know the patterns. We see the costs. It's time to try something different.”**

Thank you.



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