Establishing the Context: Draft Quality by Design "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?

https://www.ctti-clinicaltrials.org/website-administration/documents/QbD%20workshop_exec%20summary_1_30_12_FINAL_v3.pdf

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.

The Challenge: Balancing Principles with Pragmatism

* **ICH 2.13** Systems with procedures that assure the quality of every aspect of the trial should be implemented.

* 5.18.3 The determination of the extent and nature … should be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the trial

The Goal of this Project

* Produce a draft document outlining:
  * High-level principles for building quality into trials
  * One potential approach to prospective quality planning

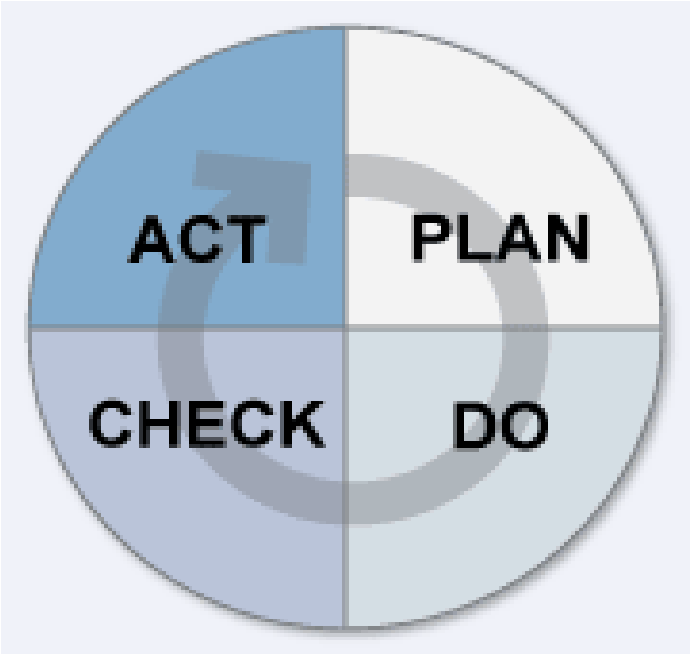
* Test the document through a series of workshops
  * Different therapeutic areas
  * Different product types
  * Various stakeholders
  * Different functional lines

The Goal of this Project

* 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

In 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

http://www.iso.org/iso/catalogue/management_standards/understand_the_basics.html

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
  * Interpretation of trial results

Examples of Errors 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

Examples of Errors that Mattered

Study Medication Packaging

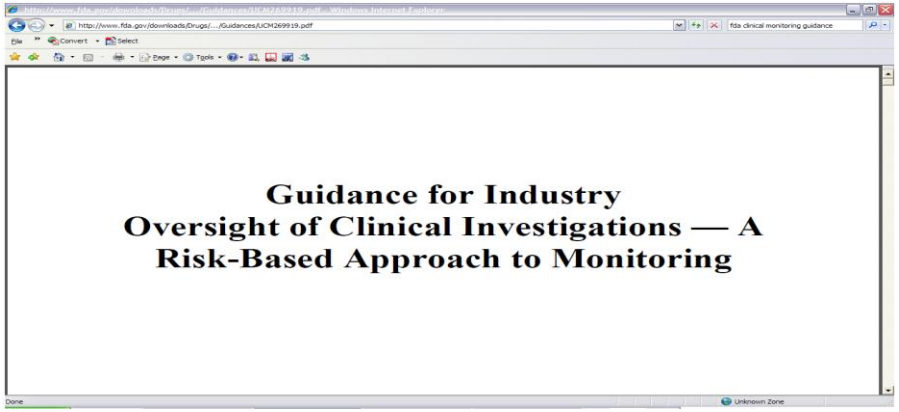
- Study drugs supplied in kits that could be used for multiple subjects
- **Each vial** in given kit was to be administered to only one subject
- Same vial was given
  - to more than one subject, and
  - on more than one occasion to the same subject
- Unable to confirm subjects received drug to which they were randomized

Where to start?

* Convened Project Working Group
  * Teleconferences May and June
  * Face-to-face meeting July

* Defined "Critical to Quality Factors" generally relevant to:
  * Integrity/reliability of conclusions based on study data
  * Safety of trial participants

But Wait…



* "The trial design and objectives will strongly influence the significance of "critical to quality" factors."
  * E.g. Data quality controls of superiority vs. inferiority trial

CTQs: Feasibility

* Study and Site Feasibility
* Accrual

CTQs: Protocol Design

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

CTQ: Patient Safety

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

CTQs: Study Conduct

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

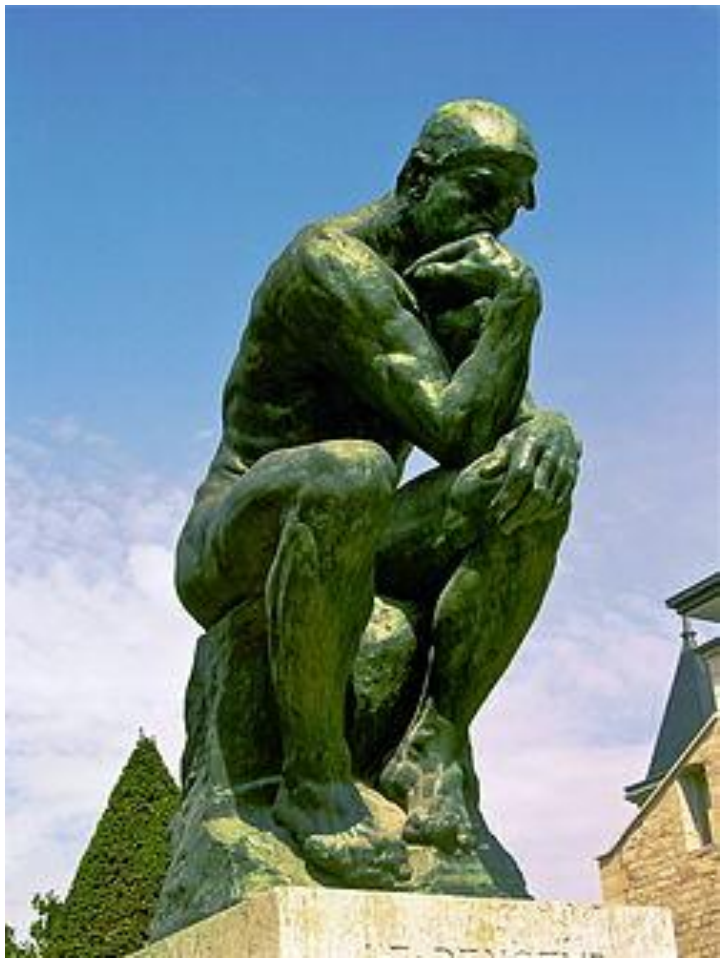
CTQ: Potpourri

* Study reporting
* Third party service providers

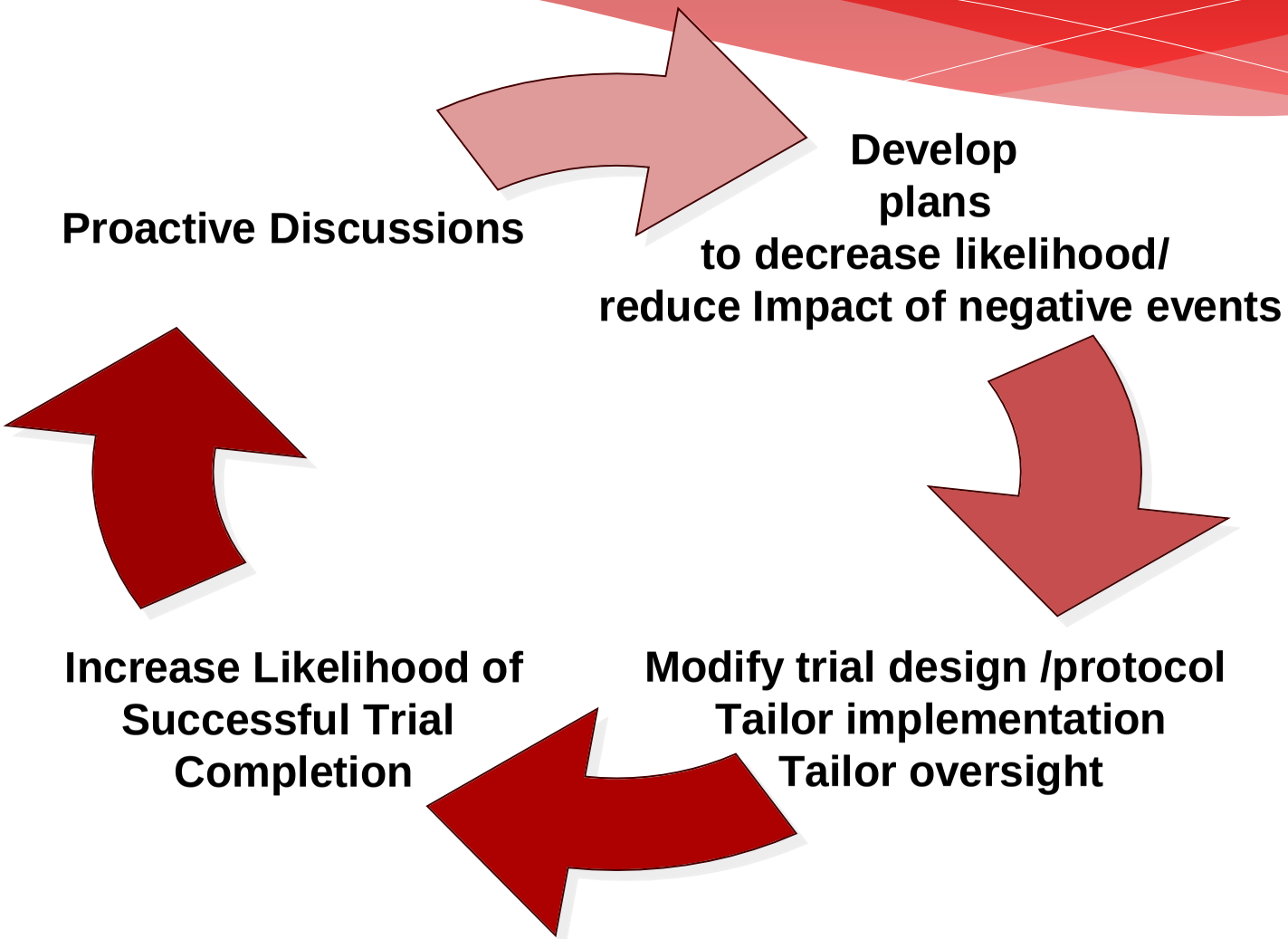
Identifying Potential Risks to Critical to Quality Factors in a Trial

* Developed series of examples for consideration for each CTQ Factor
  * Not a checklist
  * Not all-inclusive

Martin Says…



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


Proactive Discussions
Develop plans to decrease likelihood/ reduce Impact of negative events
Modify trial design /protocol
Tailor implementation
Tailor oversight
Increase Likelihood of Successful Trial Completion

Example: Data Recording and Reporting

* Will data be reported in paper CRF or via EDC?
* What opportunities are there to pilot the CRF and/or to test the usability of EDC systems?
* Will timely entry and transfer of data using EDC be feasible in all the regions in which the study will be conducted?
* Do methods for data capture allow data to be collected in parallel with the performance of the clinical routine?
* Will multiple data systems be utilized, requiring transfer and integration (e.g. central lab, IVRS, imaging reader)?
* Are the timeframes for data submission from sites and/or transfers from third-party vendors appropriate to facilitate timely internal review?

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

* **Examples**
  * Standard of care in planned countries/regions vs. study requirements
  * Access to survival data / data on subjects lost-to-follow-up
  * Burden of study procedures vs. impact on enrollment

Examples: Eligibility Criteria

* Are all criteria relevant to ensuring the specific subject population needed for the trial?
* Is there a need to assess the effectiveness and safety of the investigational product (IP) in a real-world population?
* Are there clear criteria to define the population (e.g. criteria for "atrial fibrillation" or "diabetes")?
* What is the impact of "getting it wrong" with regard to a specific criterion? Would a subject be removed? Replaced?
* Do any eligibility criteria require information to be submitted to/received from third parties external to the site (e.g. an image read)?

Example: Study Endpoints

* How and by whom will the endpoint(s) be ascertained?
* What measures are needed to ensure appropriate endpoint ascertainment and reporting if an endpoint is expected to occur external to the site?
* Is the endpoint clearly defined, such that it may be consistently ascertained across subjects over the course of the study?
* Is the endpoint objective (e.g. pregnancy, death) or subjective? If it is a "soft" endpoint, how will the potential for bias to be introduced be minimized?
* Are endpoints being adjudicated by an independent committee to address potential for bias, and what processes are critical to this adjudication?
  * Adjudication rules and required training?
  * Events are appropriately sent for adjudication?

Thank you!

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