This slide deck provides introductory materials for a QbD workshop to allow attendees to model the QbD Process.
## Workshop Agenda

<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
<th>Facilitator</th>
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<tbody>
<tr>
<td>[15 minutes]</td>
<td>WELCOME AND INTRODUCTIONS</td>
<td>All</td>
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<tr>
<td>[45 minutes]</td>
<td>CLINICAL QBD RATIONALE AND PRINCIPLES</td>
<td>Facilitator</td>
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<td></td>
<td>Review the key drivers for quality in clinical trials</td>
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<td></td>
<td>Discuss the CTTI Quality by Design Project</td>
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<td>Review the regulatory perspective on methods to build</td>
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<td>quality into trial design</td>
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<tr>
<td>[45 minutes]</td>
<td>PRINCIPLES DOCUMENT REVIEW</td>
<td>Facilitator</td>
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<td>[30 minutes]</td>
<td>REAL-LIFE WORLD EXAMPLE</td>
<td>Facilitator</td>
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<td></td>
<td>Review examples of clinical trials that have incorporated</td>
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<td>risk-based QbD approaches</td>
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<td>Discuss the advantages and the challenges of adopting</td>
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<td>this approach</td>
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Proposed Agenda for a daylong Workshop. May be split across multiple days depending on attendee availability. Include sufficient time in each Session for Q&A / group discussion.

Have attendees introduce themselves and their role / function within the company.
<table>
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</table>
| [60 minutes]      | **BUILDING QUALITY IN TO A CLINICAL TRIAL - CASE STUDY:** BREAKOUT SESSION 1  
                   Working in groups, participants will apply the Quality by Design principles to the hypothetical protocol outline, taking into account the concerns of key stakeholders. Each group will select the top 5 factors that are critical to the success and quality of the trial and describe why they are important. | Individual groups / Breakout Session Facilitators |
| [Plan for 15 minutes per group] | **BREAKOUT SESSION 1 – GROUP REPORT OUT**  
                   Workgroup feedback: Present and discuss the approach to identifying “critical to quality” parameters taken by each workgroup (15 minutes each) | Group Spokespeople / Facilitator                 |
| [60 minutes]      | **BREAKOUT SESSION 2**  
                   Select one critical to quality parameter identified in the previous breakout session and address the following:  
                   • What are the risks related to this critical to quality parameter?  
                   • What proactive steps can be taken to avoid problems?  
                   • What ongoing checks can be performed to detect problems?  
                   • What type of error will trigger corrective actions?  
                   • How will lessons learned be captured and communicated? | Individual groups / Breakout Session Facilitators |
| [Plan for 15 minutes per group] | **BREAKOUT SESSION 2 – GROUP REPORT OUT**  
                   Present and discuss the approach to identifying “critical to quality” parameters taken by each workgroup (15 minutes each) | Group Spokespeople / Facilitator                 |
| 30 minutes        | **IMPLEMENTATION**  
                   1. Review CTTI toolkit  
                   2. Discuss any barriers to widespread adoption of the QbD approach within [] and identify actions to address these barriers. | Facilitator All                                  |
| 15 minutes        | **NEXT STEPS AND CLOSING REMARKS** | Facilitator                                     |
CTTI Quality by Design Project Background
Key Driver for Clinical QbD

If you are in a shipwreck and all the boats are gone, a piano top buoyant enough to keep you afloat that comes along makes a fortuitous life preserver. But this is not to say that the best way to design a life preserver is in the form of a piano top.

I think that we are clinging to a great many piano tops in accepting yesterday’s fortuitous contriving as constituting the only means for solving a given problem.....

*Operating Manual for Spaceship Earth*, Buckminster Fuller; 1968

Clinical trials are essential to the evaluation of promising scientific discoveries, but they are becoming unsustainably burdensome, threatening to deprive patients and health-care providers of new therapies and new evidence to guide the use of existing treatments.

Key Elements Identified by FDA and EMA

Simply advocating the “highest level” of quality has little practical meaning in itself.

The cost associated with incremental improvements in quality becomes ever higher as perfection is approached and becomes disproportionate to any addi
Origins of the Clinical Trials Transformation Initiative (CTTI) Quality by Design Project

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?
Re-Framing Quality

“Quality” is the absence of errors that matter to decision-making

i.e. errors that have a meaningful impact on the safety of trial participants or credibility of the results (and thereby the care of future patients)

Key point: To do this, we need to reframe how we describe quality. We need to define quality as...

Recognize that the errors that matter most may differ by audience (what matters to a patient to a clinician to a regulator, etc.)
Example: An Error that Mattered (Delay in Approval)

- Filing review revealed easily detected errors in data related to safety parameters.
- Errors associated with scanning of paper CRFs.

Site Entry: 002
Line listing: 092

Submission to FDA had easily detectable errors. Safety data – in this case Units of Hemoglobin transfused – had clinically implausible entries (92!). In looking further, the errors had to do with scanning of paper CRFs.
Why did it happen?

Sponsor vs. CRO

- Pervasiveness of errors uncertain at filing for both parties
- Lack of clarity on responsibilities for data management
  - Creation / maintenance of data management plan
  - Routine data management QC during study conduct
  - Pre-filing data quality assessment

Lack of prospective dialogue and agreement on sponsor/CRO responsibilities for data management – an avoidable error.
CTTI QbD Project Plan

- Produce a draft document outlining:
  - High-level principles for building quality into the design and operations of trials
  - One potential approach to prospective quality planning

- Test and refine the document through a series of workshops
  - Different therapeutic areas and product types
  - Model prospective, cross-functional dialogue, including input from investigators, patients, health authorities and others with a stake in trial conduct

- Evaluate the workshops’ impact and disseminate the initial results

- Encourage and support further development and implementation

Key point: To prevent avoidable error and as part of the “Principles” document advocated in Aug 2011, the CTTI project team planned the following activities…
Quality by Design (QbD)

Protocol (Plan)
- assess key risks (likelihood, impact)
- plan mitigation
- plan evaluation

Operations (Do)
- organization, training, systems and procedures tailored to the protocol

Monitoring (Check)
- measure and evaluate performance

Make improvements (Act)
- re-assess risks
- make appropriate changes to protocol, operations or monitoring

Key point: QbD is based on the Deming Cycle – Plan Do Check Act (or Plan Do Study Act)

Landray et al DIJ 2012
Key Drivers of Quality in Clinical Trials

Slides c/o Martin Landray
High quality clinical trials

Avoid errors that matter to decision making

Human subjects protection
  ▪ appropriate information & consent at each stage
  ▪ safe administration & monitoring of investigational products
  ▪ safe study procedures & investigations

Reliability of results
  ▪ detect true effects (efficacy, safety)

Wider environment
  ▪ participants in other trials
  ▪ public health (including patients not in trials)
  ▪ physical environment
Impact of errors on the credibility of results

Random Errors

- affect the precision of estimates (adding “noise” and reducing statistical power), but will not introduce bias in either direction

[Note: For equivalence assessments, random errors are counter-conservative]

Systematic Errors

- lead towards a particular decision
Avoid undue emphasis on data points

Reliable RESULT ≠ Accurate DATA

Accurate DATA ≠ Reliable RESULT
Reliable assessment of treatment effects

1. Recruitment
2. Randomization with Allocation Concealment
3. Compliance with allocated treatment
4. Capture of relevant events in appropriate detail
5. Analysis by allocated treatment
Focus on What Matters: Recruitment

Inclusion criteria

- relevant to target population
- at sufficient risk of the key outcomes
- (not the same as participant characterization)

Exclusion criteria

- human subjects protection
  - focus on comorbidity, concomitant medication, consent
  - avoid unnecessary criteria

Uncertainty principle

- if uncertain whether the treatment is indicated (or contra-indicated), randomize

Feasible

- must fit with routine care: clinicians are busy, patients are sick
Key features for reliable assessment of moderate treatment effects

Proper randomization
- no foreknowledge of likely treatment allocation

Relevant outcomes
- sufficient numbers
- recorded with appropriate accuracy
- adequate timescale

Appropriate follow-up
- meaningful treatment difference
- minimize post-randomization withdrawals
- minimize loss to follow-up (e.g. after 1st event occurs or study treatment stops)

Unbiased ascertainment and analysis of study outcomes
- focus on robustness of result, not precision of data points
- comparisons with the randomized control group
  (except for assessing big effects on rare events)
- avoid emphasis on subgroups and on non-randomized “on-treatment” analyses
Focus on What Matters: Unbiased treatment allocation & follow-up

- No foreknowledge of likely treatment allocation
- Meaningful treatment difference
- Minimize post-randomisation withdrawal
  (i.e. intent-to-treat)
- Minimize losses to follow-up (e.g. after primary event occurs or study treatment stops)
Focus on what matters: Randomization
Focus on What Matters: Investigational Product Compliance

- **Non-compliance**
  - Active group doesn’t receive / stops investigational product
  - Active group starts other treatment (e.g. effective comparator)
  - Control group receives investigational product

- **Impact on results**
  - less difference between randomized groups
  - conservative for superiority assessments
  - counter-conservative for non-inferiority / safety assessments
Focus on What Matters: The Patient Perspective

What do the 2 alternative interventions involve?
- is there really uncertainty about how to treat this?
- how quickly will I be able to work (type, drive, fly)?
- what about long-term function (e.g. piano, cello, arthritis)
- if I am randomized to one intervention, will I regret that I didn’t get the other?

How much effort will this be for me?
- e.g. visits, forms, X-rays

Is the trial likely to provide a useful answer?
- is it focussing on an important outcome?
- is it sufficiently large? how is recruitment going?
Summary

Objective: Improve the availability of reliable information on important healthcare decisions

Design quality in to the trial protocol and procedures

Identify and address risks as trial progresses

Focus efforts to enhance quality (including monitoring):
- Appropriate to the setting
- Proportionate to the risks
- Foster improvement

Be open about quality assurance
- Share management plans and issues identified
The Regulatory Perspective
Maximally efficient, agile clinical development programs that reliably produce **high quality data** and protect trial participants without extensive regulatory oversight.”

- Janet Woodcock, MD
  CTTI Monitoring Workstream #3 Workshop
Another Perspective

*If everything is under control, you are moving too slow.*

- Mario Andretti
Are we there yet?
Analysis of OSI Reviews of Marketing Applications Indicates Opportunities for Improvement Remain

104 original and supplemental NDAs/ BLAs reviewed by OSI from 1QFY10 to 1Q FY11

- Significant data integrity concerns affected 5 inspected applications (5%)
- Some systemic errors persisted due to deficits in sponsor monitoring, but had a root cause in study design and planning.
- For 2/5 applications, concerns arose solely from **internal processes** at the sponsor and CRO, unrelated to clinical investigator activities

1. Meeker-O'Connell and Ball
   FDLI Update 2011;2: 8-12
You start out with a beautiful green tree that should be admired and then everybody in the family wants to put an ornament on it… and no one will take grandma’s ornament off the tree. So you end up with a protocol that is impossible to do and is very distracted from answering the question you originally had.”

- Dr. Robert Califf, Mind the Gap seminar, “Innovative Approaches to Clinical Trials.”
Building Quality into Clinical Trials

Quality cannot be monitored, audited, or inspected in retrospectively

“The most important tool for ensuring human subject protection and high-quality data is a well-designed and articulated protocol.”

FDA Draft Clinical Monitoring Guidance (published 29 August 2011)

At the trial level, the protocol – or more appropriately the investigational plan -- is the blueprint for quality
Building Quality into the Scientific and Operational Design of Trials

- Prospectively identify the aspects of a trial that are “critical to quality”

- Identify important and likely risks to “critical to quality” aspects

- Tailor the investigational plan and trial implementation to eliminate or reduce the impact of “errors that matter”
The Principles Document
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 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.”
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 study 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

<table>
<thead>
<tr>
<th>Principles Document V1.0 (Sept 2012)</th>
<th>Principles Document V2.0 (Jan 2013)</th>
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<tbody>
<tr>
<td>• Identified CTQ Factors</td>
<td>For each CTQ Factor, split “examples for consideration” into two categories:</td>
</tr>
<tr>
<td>• Grouped Factors into 7 categories</td>
<td>• Potential Considerations in Evaluating Relative Importance of CTQ Factor</td>
</tr>
<tr>
<td>• Developed series of “examples for consideration” for each CTQ Factor</td>
<td>• Examples of Issues to Consider in Evaluating Risks to CTQ Factor</td>
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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
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…
Trial Design Matters When Evaluating CTQs

“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
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 measurable criteria to define the population?

- Is there a particular criterion critical to subject evaluability (e.g. for an enrichment design) or to subject safety?
Example: Blinding

Relative Importance

> Is this a blinded study, and if so, what is the impact of unblinding on interpretation of outcomes?

> Who does the study require to be blinded vs. unblinded, and what are the processes and responsibilities for maintaining the blind?

Potential Risks

> Opportunities for blind break – critical failure points

> Complexities of processes to maintain the blind
Thinking About Blinding Broadly

What are the potential points of unblinding?

Example

- Efficacy endpoint: independent review committee
  - Radiologist (read)
  - Medical oncologist (confirm)

- Clinical information for oncologist review submitted to sponsor for redaction and provision to oncologist.

- Charter requires specific information to be redacted prior to provision to oncologist.
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
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?
CTQs: Potpourri

- Study reporting
- Third party service providers
Many ideas grow better when transplanted into another mind than the one where they sprang up.”

- Oliver Wendell Holmes
Closing thoughts today

“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.”
Today’s case study
Critical to Quality Factors – Case Study

Remember Fergus Sweeney’s rule: If you had $500 to spend, where would you spend it…

1. <>
2. <>
3. <>
4. <>
5. <>
Reflection: The Path Forward for CTTI and QbD
Evaluation of Workshops

CTTI invited 21 workshop attendees to participate in a one-hour long telephone interview to discuss the application of QbD principles in their organizations.

RTI completed 19 structured interviews from June 9th - July 14th.

Workshop was overwhelmingly described as helpful and well-run
- The case study activity was consistently referenced as particularly helpful
- Participants valued hearing from regulators and other organizations
- Most reported they were able to apply what they learned, but the impact in their organizations varied
One Key Challenge

Organizations believe in QbD/QRM but are struggling to implement.

- Participants regularly stated that they and their organizations believed in QbD/QRM. They were convinced that it was a better way to manage clinical trials.

- However, moving from understanding QbD/QRM to doing QbD/QRM was a key challenge.

- Many participants wanted more examples of how others had implemented QbD/QRM.
Reported Barriers to Implementation

Most participants did not report any regulatory or financial barriers

- A small number alluded to a possible disconnect between the support that FDA leadership espoused for QbD/QRM principles and the actions of FDA auditors on the ground.

Nearly all participants reported cultural barriers, especially:

- Fear of change
- Difficulty overcoming organizational inertia
- Lack of understanding for the value of QbD/QRM
- Concern it would take more time and create more work
Barriers to implementation

The biggest barrier is time and the perception that this takes extra time. Getting people to step back and think about ‘going slow to go fast’ or taking time now to benefit in the end. On these studies, people feel a real sense of urgency, (they've) got to get it done.”

The biggest barrier is ‘bad habits’ of people who are used to doing things a certain way, who have to be retrained. It was 100% cultural.”

It is a huge cultural change for the monitors to limit themselves to the sections that have been agreed to be the monitored ones... and to limit themselves.”