Regulatory Science Symposium:

Quality by Design in Clinical Trials

Friday March 13, 2020, 9am – 3pm

USC School of Pharmacy
International Center for Regulatory Science
SC CTSI

Agenda

9:00 am	**Introduction** I Eunjoo Pacifici, PharmD, PhD USC, SC-CTSI, School of Pharmacy I *Chair and Associate Professor, Dept. of Reg. & Quality Sciences; Associate Director, D. K. Kim International Center for Regulatory Science*
9:30 am	**What do we mean by Quality by Design?** I Nancy Pire-Smerkanich, DRSc USC, SC-CTSI, School of Pharmacy I *Assistant Professor, Dept. of Reg. & Quality Sciences*
10:30 am	**Break**
10:45 am	**CTTI's Approach to QbD** I Eunjoo Pacifici, PharmD, PhD USC, SC-CTSI, School of Pharmacy I *Chair and Associate Professor, Dept. of Reg. & Quality Sciences; Associate Director, D. K. Kim International Center for Regulatory Science*
11:45 pm	**Lunch**
12:15 pm	**Developing QbD Tools for Clinical Researchers** I Hamid Moradi, MD, FACP, FASN UC Irvine I *Associate Clinical Professor, Division of Nephrology, School of Medicine* *Associate Director, Nephrology Fellowship Program, School of Medicine*
1:15 pm	**Integrating QbD into Team Science and Project Management for Research Success** I Allison Orechwa, PhD I USC, SC-CTSI, *Director, Programmatic Development*
2:00 pm	**Break**
2:15 pm	**Applying Design for Six Sigma** I Nick Vyas Ed.D. USC, Marshall School of Business I *Executive Director-Center for Global Supply Chain Management & Academic Director - MS in Global Supply Chain Management*
3:00 pm	**Wrap-Up** I Eunjoo Pacifici, PharmD, PhD USC, SC-CTSI, School of Pharmacy I *Chair and Associate Professor, Dept. of Reg. & Quality Sciences; Associate Director, D. K. Kim International Center for Regulatory Science*

Please email the completed survey to Apurva Uniyal (uniyal@usc.edu) to receive a certificate of completion by Friday, March 20, 2020.

Series sponsored by The Greater LA CTSA Consortium

UCLA CTSI Grant #UL1TR001881 | SC CTSI | UC•IRVINE ICTS from lab to life.

SC CTSI is part of the Clinical and Translational Science Awards (CTSA), a national network funded through the National Center for Advancing Translational Sciences (NCATS) at the NIH (Grant Number UL1TR001855). Under the mandate of "Translating Science into Solutions for Better Health," SC CTSI provides a wide range of services, funding, and education for researchers and promotes online collaboration tools such as USC Health Sciences Profiles.

Regulatory Science Symposium:

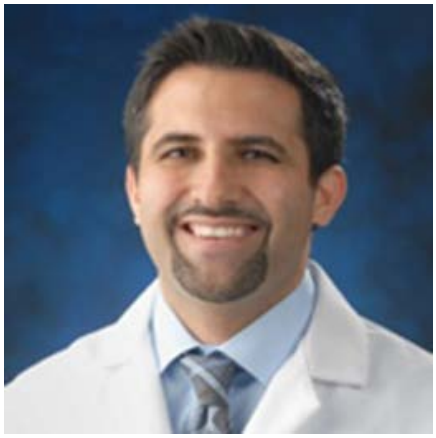
Quality by Design in Clinical Trials

Speaker Bios

Eunjoo Pacifici, PharmD, PhD, is the Chair and Associate Professor of Regulatory and Quality Sciences and Associate Director of International Center for Regulatory Science. Dr. Pacifici received her BS in Biochemistry from UCLA followed by PharmD and PhD in Toxicology from University of Southern California. She conducted her graduate research in the laboratory of Dr. Alex Sevanian in the Institute for Toxicology at USC where she studied the mechanism of oxidative damage and repair in endothelial cell membrane. Before returning to USC as faculty, Dr. Pacifici worked at Amgen and gained experience in conducting clinical research with special focus on Asia Pacific and Latin America region. She initially worked in the clinical development group managing U.S. investigational sites and central laboratories and then went on to work in the Asia Pacific/ Latin America group interfacing with local clinical and regulatory staff in Japan, People's Republic of China, Taiwan, and Mexico. She represented regional clinical and regulatory views on therapeutic product development teams and led satellite task forces in order to align local efforts with U.S. activities. Her additional professional experiences include community pharmacy practice in various settings and clinical pharmacy practice at the Hospital of the Good Samaritan in Los Angeles. Her current focus is on developing the next generation of regulatory scientists and pharmacy professionals with the knowledge, tools, and skills to expedite the development of innovative, safe, and effective biomedical products. epacific@usc.edu

Nancy Smerkanich, DRSc, **MS,** is an Assistant Professor, Department of Regulatory and Quality Sciences in the School of Pharmacy at the University of Southern California (USC).Dr. Smerkanich received her faculty appointment after successfully completing her Doctoral Dissertation on "Benefits Risk Frameworks –Implementation in Industry" in 2015. In addition to teaching in courses related to drug development and clinical trials, she continues to provide regulatory guidance to industry peers. Nancy brings many years of practical regulatory knowledge and experience to academia where she participated in all regulatory aspects of product development, having served as Regulatory Liaison, US Agent, and Global Regulatory Lead across all therapeutic areas. Known for her dedication to education and mentoring across industry, Nancy continues to be recognized for her ability to provide accurate, relevant and dynamic instruction on both the technical and strategic aspects of global regulatory affairs and for her service to professional organizations such as the Drug Information Association (DIA) and The Organization for Professionals in Regulatory Affairs (TOPRA).piresmer@usc.edu. With over 30 years of experience, Dr. Smerkanich has participated in all regulatory aspects of drug development, having served as Regulatory Liaison, US Agent, and Global Regulatory Lead across all therapeutic areas. Prior to joining Octagon, Dr. Smerkanich held various Regulatory Affairs positions within industry, including nine years at Merck and seven years as an independent consultant. Dr. Smerkanich holds a Doctorate and Master's degree in Regulatory Science from

USC and Bachelor of Science Degree in Microbiology and a Bachelor of Arts in Russian from the University of Connecticut. piresmer@usc.edu



Hamid Moradi, MD, is an Associate Director of Nephrology Fellowship Program, Medicine School of Medicine Associate Clinical Professor, Division of Nephrology, Hypertension & Kidney Transplantation at the University of California, Irvine. Dr. Hamid Moradi is a nephrologist in Orange, CA and is affiliated with multiple hospitals in the area, including UC Irvine Medical Center and VA Long Beach Healthcare System. He received his medical degree from Oregon Health & Science University School of Medicine and has been in practice 15 years. He specializes in acute kidney injury, chronic kidney disease and dialysis, and glomerular disease and is experienced in glomerular disease. His research has focused on deciphering novel pathways which can be targeted to improve survival in end stage kidney disease (ESKD) with a focus is on lipids, lipid metabolism and alterations of endocannabinoid system in advanced chronic kidney disease. hmoradi@uci.edu

Allison Orechwa supports the development of new programs and services at SC CTSI in collaboration with faculty leaders and program staff. Her projects have included the new Clinical Research Support group, USC's research data warehouse, and the implementation science collaboration with UCLA and LA County Department of Health Services. Prior to the SC CTSI, Dr. Orechwa worked as an Education Research Analyst in the Standards and Review Office of the U.S. Department of Education. She earned a PhD from USC in cognitive neuroscience with an emphasis on functional neuroimaging of the brain's language and reading networks. allison.orechwa@med.usc.edu

Nick Vyas, a practitioner in operations management and organizational excellence through the application of Blended Quality Management, AI, ML, RPA, Blockchain, and Data Analytics received his Doctor of Education from USC with his published dissertation on Conceptualization of Higher Education Excellence System (HEES): Use of Advance Data Analytics and Blended Quality Management. A Subject Matter Expert in End-to-End Global Supply Chain Management (GSCM), Dr. Vyas has led cultural and business transformation for fortune 100 companies. As USC Marshall Center for GSCM's Executive Director / Co-founder, Director of MS GSCM and as an Assistant Professor, he was awarded with the Golden Apple Award for teaching excellence and recognized as a "Supply Chain Leader" for the APICS Excellence Awards. As a thought leader, he speaks at conferences sharing his views on global trade, disruptive technology and GSCM. Dr. Vyas serves to make GSCM education accessible through the Gift of Knowledge and Supply Chain Professionals Without Borders. nikhilvy@marshall.usc.edu

Regulatory Science Symposium

"Quality by Design in Clinical Trials"

Introduction

Eunjoo Pacifici, PharmD, PhD

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Symposium Log-In

Regulatory Science Symposium:

Quality by Design in Clinical Trials

Friday March 13, 2020, 9am – 3pm

To meet the university's public health requirements, the Department of Regulatory and Quality Science **has moved this onsite event to a DIGITIAL PLATFORM**. The **Zoom** platform allows for live-streaming of presentations, audience interaction, and polling. Prior to the presentation, please take a few minutes to download Zoom by clicking the link below:

Live Stream Link

We will start presentations promptly at 9am.

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A single stop for accessing all services an Investigator and research team needs to develop, activate, conduct, and report results for human subject research studies

Initial focus on investigator-initiated trials (non-cancer)

- **Services:**
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  - Recruitment support
  - Budget preparation support
- **Clinical Trials Unit (CTU)**:
  - Skilled research and nursing staff
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  - Specimen processing lab
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https://sc-ctsi.org/about/groups/clinical-research-support

Nicki Karimipour, PhD
- Interim Associate Director
- crs@sc-ctsi.org

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Symposiums

- **2015 -** Clinical Trial Hurdles
- **Spring 2016** - Clinical Trial Startup
- **Fall 2016** - Monitoring and Auditing
- **Spring 2017** - Clinical Trials in Special Populations
- **Fall 2017** - Clinical Trials in Era of Emerging Technologies and Treatments
- **Spring 2018** - Regulatory Aspects of Clinical Trial Design
- **Fall 2018** - Pharmacovigilance and Safety Reporting
- **Spring 2019** - Patient-Centered Drug Development and Real World Evidence/Data
- **Summer 2019** - Clinical Trials with Medical Devices
- **Fall 2019** - Legal Aspects of Conducting Clinical Trials
- **Spring 2020** - Quality by Design in Clinical Trials
- **Fall 2020 - To Be Determined**

Symposium lectures are packaged and available at SC-CTSI website: https://sc-ctsi.org/training-education/courses?audience=researchProfessionals&competency=regulatory-science&q=

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Help us select the next symposium topic!

Ethical Issues in Clinical Trials

IND and IDE: Requirements, Application and Process

Post-Marketing Evaluations / OTC and Generic Drugs

Project Management in Clinical Research: Operationalize Protocol

Medical Device Pipeline/Legal Elements of Biomedical Commerce

Regulation and Management of Data and Specimen Biorepositories

US and International Research/Trial Regulation Differences

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Regulatory Science Symposium Series

"Quality by Design in Clinical Trials"

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Today's Agenda

09:00 am	**Introduction** | Eunjoo Pacifici, PharmD, PhD USC, SC-CTSI, School of Pharmacy I Chair & Associate Professor, Dept. of Reg. & Quality Sciences; Associate Director, D. K. Kim International Center for Regulatory Science
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11:45 am	**Lunch Break**
12:15 pm	**Adoption and Implementation of QbD at Academic Health Centers** I Hamid Moradi, MD, FACP, FASN UC Irvine I Associate Clinical Professor, Division of Nephrology, School of Medicine, Associate Director, Nephrology Fellowship Program, School of Medicine
1:15 pm	**Integrating QbD into Team Science and Project Management for Research Success** I Allison Orechwa, PhD I USC, SC-CTSI, Director, Programmatic Development
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Presented by the USC School of Pharmacy International Center for Regulatory Science and the Southern California Clinical and Translational Science Institute

This certifies that

Before the end of todays Symposium you will receive an electronic copy of the program evaluation.

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Eunjoo Pacifici, PharmD, PhD
Director
International Center for Regulatory Science

Thomas A. Buchanan, MD
Director
Southern California Clinical and Translational Science Institute

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Quiz Time!

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"Quality" in clinical trials is defined as:

Ensuring the trial is conducted according to protocol, GCP, SOP, and regulatory requirements

The absence of errors that matter to decision making

Ensuring all data collected for a study has been verified for accuracy

The absence of data corrections without proper initials and dating

What sector first originated the idea of quality by design?

Research

Farming

Manufacturing

Healthcare

Why is Quality by Design important?

It expedites site initiation and subject accrual

It expedites patient retention and study completion

It retrospectively reviews clinical trial data to determine if the study findings are robust

It prospectively examines the objectives of a trial and define factors critical to meeting these objectives

Three key principles of quality science include quality of end product, culture of productivity, and focus on consumer feedback.

True

False

Which of the following is NOT a QbD recommendation from CTTI?

Focus efforts on activities essential to credibility of outcomes

Focus on creating useful tools and checklist

Involve broad range of stakeholders in protocol development

Prospectively identify and periodic review quality factors

What is an example of a factor critical to quality?

Path to reimbursement for innovative products

Design of the study protocol

Time to study initiation

Completion of study enrollment

Understanding what is critical to quality results in a focused monitoring and auditing plan.

True

False

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What is not a barrier to QbD implementation?

Difficulty overcoming organizational inertia	A
Fear of change	B
Concern it would take more time and create more work	C
Lack of understanding in QbD value	D
All of the above are barriers	E

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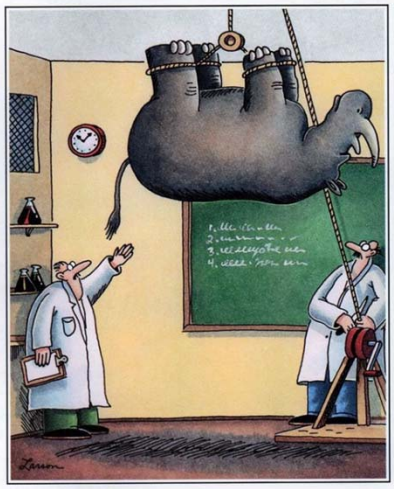
Has QbD been applied to this experiment?



Testing whether or not rhinos land on their feet

What's QbD?

Definitely!

Maybe …

No way!

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What do we mean by Quality by Design?

Nancy Pire-Smerkanich, DRSc, MS

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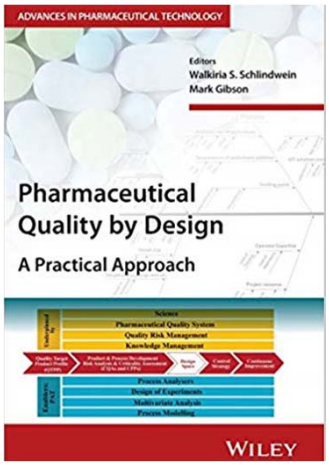
What is Quality by Design (QbD)?

What QbD is:

- A Quality System for managing a product's lifecycle
- A regulatory expectation
- Intended to increase process and product understanding and thereby decrease patient risk
- A multifunctional exercise

What QbD is NOT:

- New
- Originally used for manufacturing



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History of QbD

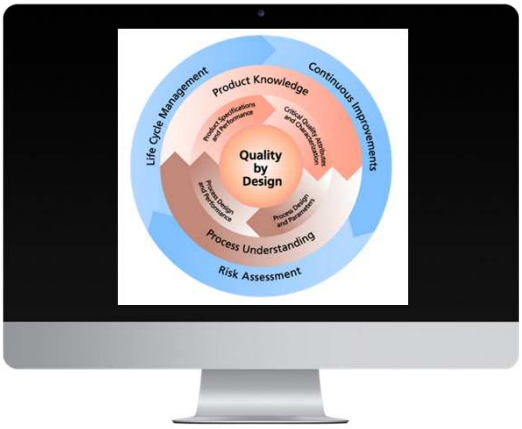
1979
Quality is Free (P. Crosby)

1982
Quality, Productivity and Competitive Positions (WE Deming) – Cease dependence on inspection to achieve quality – build into the "product" in the first place!

1987
FDA first Guideline on Process Validation

1991
Quality by Design (J Juran)

2005
ICH QbD related drafts issued (ICH Q8-11)



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Quality by Design – The Juran Trilogy

Quality Planning
- Establishing quality goals
- Developing products/processes required to meet those goals

Quality Control
- Evaluating actual performance against quality goals and
- Taking corrective action where necessary.

Quality Improvement
- Raising quality performance to unprecedented levels

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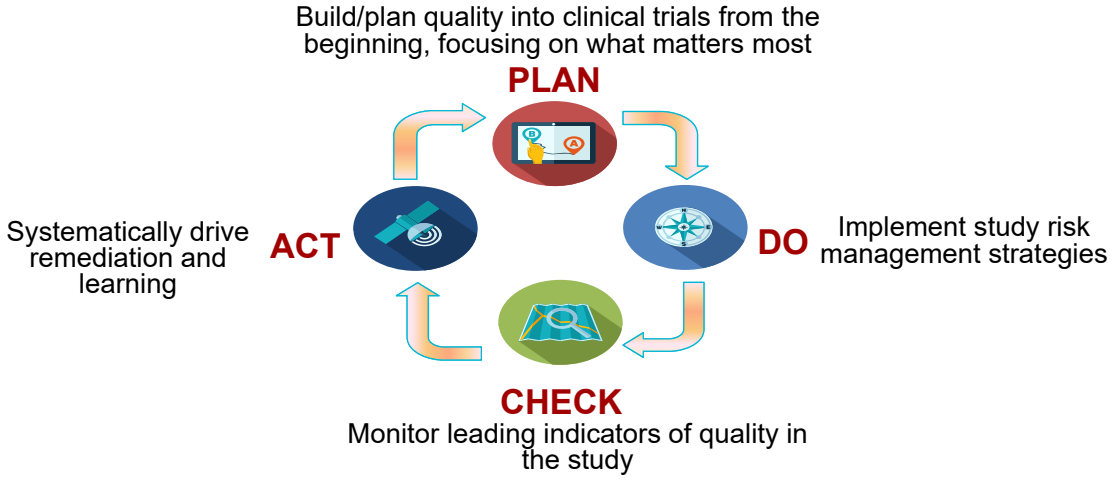
QbD Implementation: Plan, Do, Check, Act



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ICH Guidelines - Manufacturing

- ICH Q9, Quality Risk Management
- ICH Q10, Pharmaceutical Quality System
- FDA Guidance for Industry: Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations

"Quality should be built into the product, and testing alone cannot be relied on to ensure product quality."

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ICH Guidelines - GCP

The clinical corollary…

- Quality should be built into the clinical trial,
- Critical quality attributes/metrics for study data is built upon Good Clinical Practices (GCPs)
- Audit/inspection (or post hoc rework) cannot be relied on to ensure trial quality

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Quality by Design: QbD Defined

"Quality" in clinical trials is defined as the absence of errors that matter

Prospectively examining the objectives of a trial and defining factors critical to meeting these objectives

… focusing effort on those "errors that matter" for the success of the clinical trial

… taking action to prevent important risks to these critical factors from negatively impacting outcomes

Understanding what data and processes underpin a successful trial is essential to subsequently identifying and managing important and likely risks to **improve quality and outcomes for clinical trials**

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How QbD Improves Clinical Trials

QbD helps organizations become *prospectively and fully aware throughout the trial lifecycle* of the important errors that could jeopardize the ability to …

Protect patients during the trial

Obtain reliable results and meaningful information from the trial

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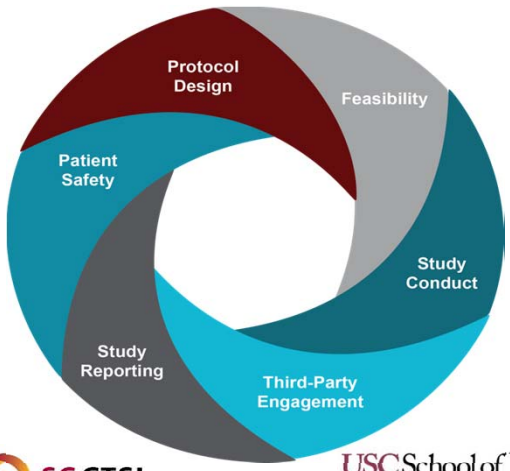
QbD Step 1

Identify "critical to quality" factors (CTQs) for your specific trial



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QbD Step 2

Discuss potential risks related to each CTQ identified that impact study quality (i.e., participant safety or credibility of results)

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QbD Step 3

Mitigate those risks that will likely lead to errors that matter and determine how to rapidly identify and react when there is an issue

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Bringing QbD Into an Organization

Focus on what matters	○ "Quality" is defined as the absence of errors that matter ○ Determine what matters for the specific trial
Develop a quality management plan	○ Initiate plan in parallel with protocol development ○ Focus on areas of highest risk for generating errors that matter
Assess performance in important parameters	○ Prospectively measure error rates of important parameters ○ Tailor the monitoring approach (e.g., site visits, central, statistical) to the trial design and key quality objectives
Improve training and procedures	○ Base on measured parameters
Report findings of quality management approach	○ Include issues found, actions taken, impact on analysis, and interpretation of results ○ Incorporate into regulatory submissions and publications

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FDA Point of View (per J Mulinde)

- FDA supports and encourages development of systematic approaches that aim to improve clinical trial quality and efficiency
- FDA recommends a Quality Risk Management approach to clinical trials

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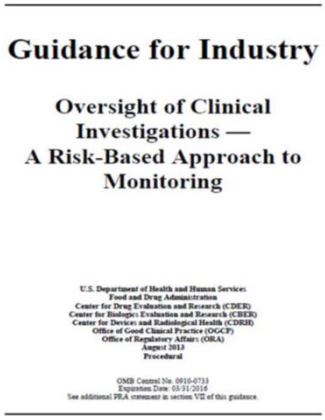
FDA Point of View (per J Mulinde)

- Protocol be considered blueprint for quality
- Conduct of a risk assessment to identify and evaluate risks to critical study data and processes
- Monitoring is one aspect of the processes and procedures needed
  - Monitoring plan be designed to address important and likely risks identified during risk assessment and discourages “One Size Fits All” approach to monitoring



Guidance for Industry

Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Office of Good Clinical Practice (OGCP)
Office of Regulatory Affairs (ORA)
August 2013
Procedural

OMB Control No. 0910-0733
Expiration Date: 03/31/2016
See additional PRA statement in section VII of this guidance.

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Cause of Errors

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
  - Reliance on eCRFs to prevent errors

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Examples of Errors

Paper CRFs→ scanning resulted in errors

- Filing review revealed easily detected errors in data related to safety parameters

Site Entry: 002

Line listing: 092

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Examples of Errors

eCRF design flaws → resulted in erroneous data collection

Consider "Signs/symptoms" for secondary endpoint

- Screen design confused sites – these were the choices:
  - (5) Resolved
  - (4) Worse
  - (3) Improved
  - (2) Same
  - (1) New

- Widespread discrepancies in data entry
- Audit trails incomplete

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Global Attention on Quality

ICH E6(R2) Addendum to Good Clinical Practices – Goals

- Better facilitate broad and consistent international implementation of new methodologies
- Innovative approaches that emphasize upfront assessment of risks specific to a study design and protocol
    - Quality risk management
    - Quality-by-design processes

Quality Focused Guidance and Activities

- Sensible Guidelines for the Conduct of Clinical Trials meetings, 2007-2012
- European Medicines Agency (EMA), Reflection Paper on Risk Based Quality Management in Clinical Trials, 2013
- Japanese Ministry of Health, Labour and Welfare (MHLW), Fundamental Notion on Risk Based Monitoring in Clinical Trials, 2013
- TransCelerate BioPharma, Inc. Risk-Based Monitoring, Quality Management Systems
- Clinical Trials Transformation Initiatives (CTTI) on Quality by Design

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International Standards Organization- ISO 8402

- Defines quality as “The totality of features and characteristics of a product or service that bear on its ability to satisfy stated or implied needs”
- *What is the stated need for clinical research???*
- *Finding new treatments for patients!!!*

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QbD Recommendations

- Create a culture that values and rewards critical thinking and open dialogue about quality, and that goes beyond sole reliance on tools and checklists
  - Consistent with advice in FDA Guidance on Monitoring, which encourages a quality risk management approach to clinical trial design and operation, and discourages a one size fits all mentality
  - Applicable also to regulatory environments

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QbD Recommendations

- Focus effort on activities that are essential to the credibility of the study outcomes

  General:

  - Data produced are sufficiently accurate and reliable (fit for purpose) so they can be used for decision making
  - Insure the rights, safety and welfare of trial participants have been adequately protected

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QbD Recommendations

- Focus effort on activities that are essential to the credibility of the study outcomes

  Regulatory Perspective:

  - Scientific Question is important
  - Produce high quality evidence to inform decision making on the use of a preventative, diagnostic or therapeutic intervention
  - Insure Trial design is adequate to answer the scientific question
  - Conduct the study well so the results will be credible

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QbD Recommendations

- Involve the broad range of stakeholders in protocol development and discussions around study quality
- Prospectively identify and periodically review the critical to quality factors.

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Some Reasons for Poor Quality

- Inadequate staff training on GCPs and the protocol, mostly due to sudden increase or decrease in resources
- Poor (or lack of) supervision or quality control of task completion during the study
- Lack of protocol clarity leading to poor understanding of what is required
- Lack of quality control over collection and recording of study data

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Some Ways to Achieve High Quality in CTs

- Each person is accountable for the quality of a study.
- Create a systematic process to build in quality that makes the tasks more achievable.
- Learn from others, especially best practices.
- Conduct risk analysis early on and throughout the project increases quality.
- Communicate clearly and often

Remember - ignoring quality costs much more than addressing it continuously.

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Pfizer QbD Pilot

- Applied QbD tools and methodologies to a clinical trial for a novel potential therapeutic for the treatment of a neurological disease scheduled to start pivotal trials
- Worked with FDA/CDER/Division of Neurology Products (DNP) and Office of Scientific Investigations (OSI) to test a model for QbD in Clinical Trials

[Ref: Sprenger et al TIRS 2012]

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Pfizer QbD Pilot

- Used an Integrated Quality Management Plan (IQMP) based on three main principles:
  1. Quality is built in at the time of protocol development and systematically managed during study conduct through a process of continuous improvement.
  2. Quality goals and relevant quality metrics are prospectively identified and measured throughout the duration of the study.
  3. Risks to quality are prospectively identified, prioritized, and mitigated.

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Pfizer QbD Pilot: PDCA Methodology

Quality Objectives:

- patient safety and rights,
- data quality and trial integrity,
- compliance with the investigational plan

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Pfizer QbD Pilot: PDCA Methodology

- Identified Critical to Quality (CTQ) Requirements
  - For each CTQ one or more metrics were identified to facilitate the measurement and monitoring of quality performance during the conduct of the clinical trials
    - For each metric, target (nominal) values and upper or lower specification limits (action thresholds) were determined.
    - A metric crossing the action threshold would require Pfizer to conduct an investigation, which might include a root cause analysis to address the issue

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Pfizer QbD Pilot: Sample Metrics

Data are entered by the site into the database in a timely manner and the database is accurate and complete	Percentage of subject visits meeting data entry target timelines within 4 calendar days
	Percentage of study sites with no data outstanding greater than 30 calendar days
	Percentage of unresolved queries in the database for longer than 30 calendar days

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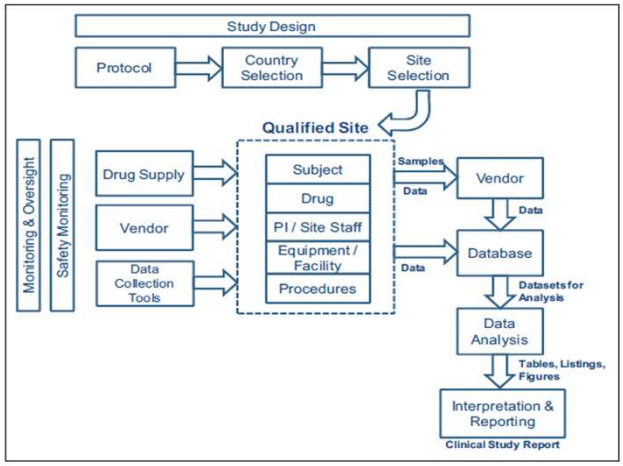
Pfizer QbD Pilot: Risk Assessment Framework – Site Focused



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Pfizer QbD Pilot: Risk Assessment

- Identified protocol specific risks associated with each operational process area OR related to critical aspects of the CT design
- Prioritized those risks based on severity, frequency of occurrence, and the ability to detect occurrence – applied a score (see next slide)
- Developed a risk management plan to reduce the occurrence of the potential cause and/or improve detection if the risk were to occur

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Pfizer QbD Pilot: Risk Assessment

Risk Level	Definitions		
	Severity	Occurrence	Detection
1	Minor impact to data quality/study integrity *or* compliance with the investigational plan	Likelihood of occurrence is remote (rare or never)	Most likely to be detected immediately
4	Minor impact to patient safety/rights, *or* significant impact to data quality/study integrity, *or* compliance with the investigational plan	May occur occasionally (sometimes)	Most likely to be detected at a quality control check point
7	Significant impact to patient safety/rights, *or* major impact to data quality/study integrity, *or* compliance with the investigational plan	May occur frequently (most of the time)	Most likely to be detected by an internal audit
10	Major impact to patient safety/rights (eg, life threatening) *or* major impact to both data quality/study integrity *and* compliance with the investigational plan	Certain to occur (all the time)	Most likely to be detected by a third-party external audit or inspection

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Some Myths about Quality

#1: Auditors are the only ones qualified to implement quality systems and processes. **no.**

#2: Maintaining a quality system is impossible with so many variables in clinical research. **no.**

#3: The cost of establishing, maintaining, and re-evaluating quality is usually very high. **no.**

#4: Quality is a department, a function, a specific role, or someone else's job. **no.**

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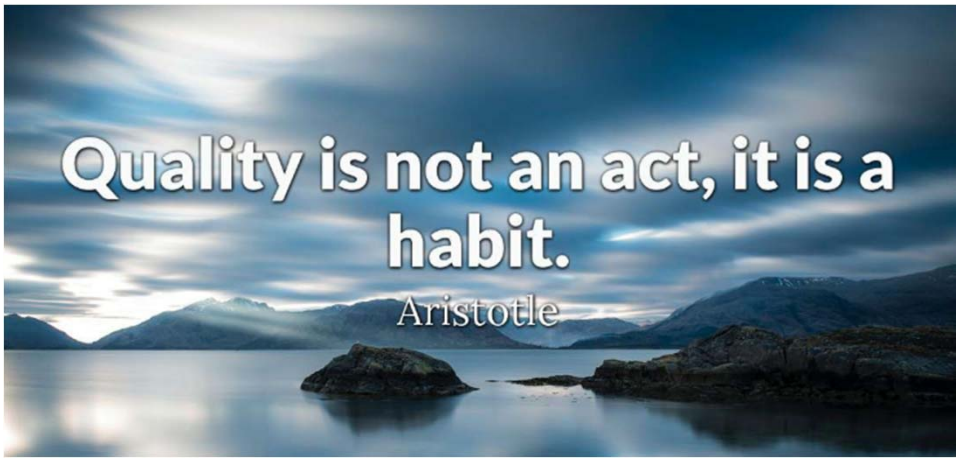
Final Thought



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Clinical Trials Transformation Initiative

Approach to Quality by Design

Eunjoo Pacifici, PharmD, PhD

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Agenda

CLINICAL TRIALS TRANSFORMATION INITIATIVE

- Clinical Trials Transformation Initiative (CTTI)
- CTTI Quality by Design Project Background
- CTTI's Approach to DbQ
- The Principles Document
  - Critical to Quality (CTQ) Factors
  - Real Word Example
  - Reflection: The Path Forward for CTTI and QbD
  - Additional Resources

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CTTI

- Clinical Trials Transformation Initiative (CTTI) is a public-private partnership co-founded by Duke University and the FDA in 2007
  - To increase quality and efficiency of clinical trials (CTs)
  - 80 member-organizations
  - Established due to concerns in CT conduct:
    - Paper-based, slow, and costly (quality and efficiency)
    - Limits number of questions that can be answered
    - Delays in access to innovations
    - Increasingly CTs are conducted outside of the U.S. and reason behind this shift needs to be understood

Origins of QbD Project

- What do we really need to get right to ensure reliability of results and patient protection?

Origins of CTTI's Work on QbD

- Current approach to trial monitoring is not effective
- 10% INDs fail to recruit a patient population appropriate to the intended use
- 3% of NDAs not approved due to missing critical data
- 25% of study procedures in phase 3 trials are not relevant to the assessment of primary endpoints
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- DiMasi JA. *Cost of developing a new drug*. http:// csdd.tufts.edu/files/uploads/Tufts_CSDD_briefing_on_ RD_cost_study_ Nov_18,_2014.pdf.
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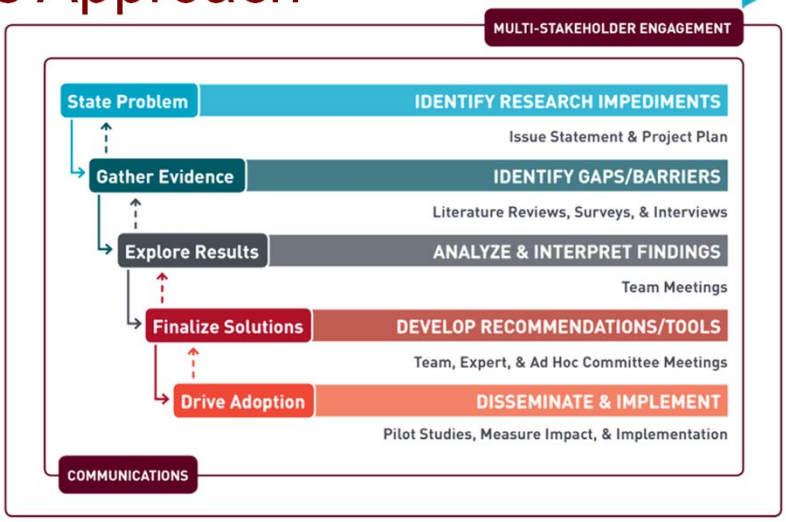
CTTI's Approach



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CTTI Activities

Quality	Patient Engagement	Investigators & Sites
○ Quality by Design ○ Informing ICH E6 Renovation ○ Diversity ○ Analysis of ClinicalTrials.gov ○ Recruitment ○ Planning for Pregnancy Testing ○ State of Clinical Trials Report ○ Monitoring	○ Patient Groups & Clinical Trials ○ Patient Engagement Collaborative	○ Investigator Community ○ Investigator Qualification ○ Site Metrics
Mobile Clinical Trials	**Novel Clinical Trial Designs**	**Ethics & Human Research Protection**
○ Novel Endpoints ○ Mobile Technologies ○ Decentralized Clinical Trials ○ Engaging Patients and Sites	○ Pragmatic Trials ○ Real-World Data ○ Registry Trials ○ Master Protocols ○ Antibacterial Drug Development ○ Large Simple Trials ○ Using FDA Sentinel for Trials	○ Single IRB ○ Data Monitoring Committees ○ Informed Consent ○ Safety Reporting

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Re-framing Quality

"Quality" in clinical trials is defined as the absence of errors that matter to decision making—that is, errors which have a meaningful impact on the safety of trial participants or credibility of the results (and thereby the care of future patients).

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CTTI QbD Recommendations

- **Create a culture that:**
  - **Values and rewards critical thinking and open dialogue about quality**
  - **Goes beyond sole reliance on tools and checklists.**
    - Dialogue about critical to quality
    - Discourage “One size fits all” approach
    - Verify quality and performance measures align with incentives
    - Culture rewards critical thinking
      - Example

CTTI QbD Recommendations

- **Focus effort on activities that are essential to the credibility of the study outcomes**
  - Evaluate study design verifying activities and data collection are essential
  - Streamline trial design
  - Identify, prevent or control errors
    - Determine essential activities to ensure trial participant safety and study result credibility
    - Eliminate nonessential activities

CTTI QbD Recommendations

- **Involve broad range of stakeholders in protocol development and discussions around study quality**
  - Engage all stakeholders with study development
  - Clinical investigators, study coordinators, site staff and patients can provide valuable insights
    - Feasibility of enrolling subjects meeting eligibility criteria
    - Study visits and procedures overly burdensome leading to early dropouts
    - General relevance of study endpoints to target patient population

CTTI QbD Recommendations

- **Prospectively identify and periodically review the critical to quality factors**
  - CTTI QbD "Principles Document" and "Toolkit"
  - Develop strategies to support quality in critical areas

  - Example:
    - Trial with major cardiovascular morbidity outcomes, strategies to ensure survival status of all participants is captured would be critical
    - But source verifying participants' temperature readings obtained as a part of vital sign assessments at routine study visits is unlikely to be considered critical to the successful outcome of the study
    - In addition, because new or unanticipated issues may arise once the study has begun, it is important to periodically review critical to quality factors to determine whether adjustments to risk control mechanisms are needed

Principles Document: Key Concepts

- Quality in clinical trials = the Absence of Errors that Matter
- Errors that have a meaningful impact on:
  - Patient safety or
  - Credibility of study results
  - Critical to quality
    - Factors that are generally relevant to the integrity and reliability of conclusions based on study data and to subject safety

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CTTI QbD: Critical Quality Factors

Protocol Design	Feasibility	Patient Safety
Eligibility Criteria Randomization Eligibility Criteria Masking Types of Controls Data Quantity Endpoints Procedures Supporting Study Endpoints & Data Integrity Investigational Product Handling & Administration	Study and Site Feasibility Accrual	Informed Consent Withdrawal Criteria and Trial Participant Retention Signal Detection and Safety Reporting Data Monitoring Committee/Stopping Rules
Study Conduct	**Study Reporting**	**Third Party Engagement**
Training Data Recording and Reporting Data Monitoring and Management Statistical Analysis	Dissemination of Study Results	Delegation of Sponsor Responsibilities Collaborations

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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?

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

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?

Example: Data Monitoring & Management

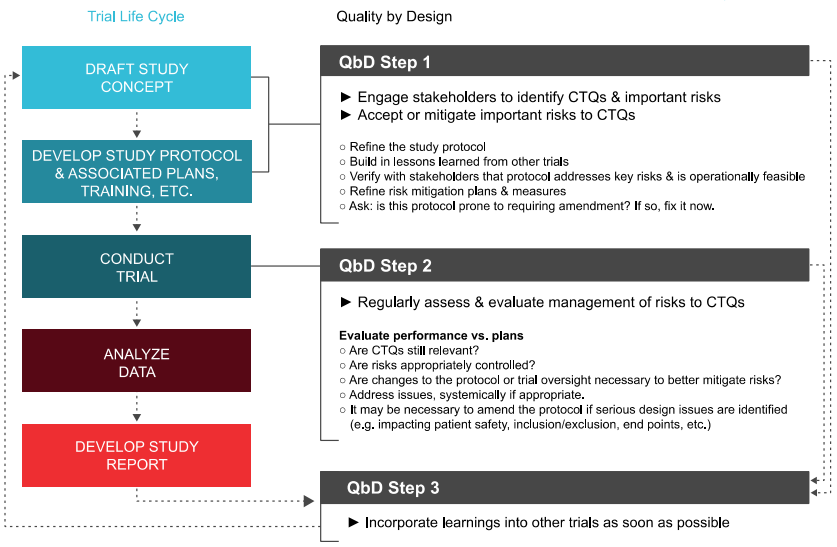
Relative Importance

- Define critical data elements for data management during protocol development.
  - *(Are there data not critical for study analyses? Why collected?)*
- 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 *where relevant*

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?

Application of **Quality by Design** in the trial life cycle



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CLINICAL TRIALS TRANSFORMATION INITIATIVE

Real World Example

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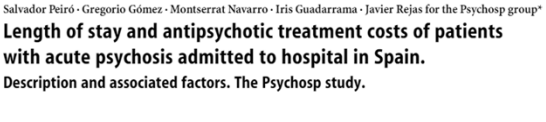
Study Overview

- A 6-Week, multi-center, double-blind, double-dummy, active-controlled randomized study to evaluate the efficacy and safety of Drug X compared to Drug Y in the treatment of patients with acute episode of schizophrenia
- Phase III trial with 10 sites (US, UK, Germany, Spain)
- 250 patients, 1-year enrollment
- Primary outcome: Change from baseline of the Positive and Negative Syndrome Scale (PANSS) total score at the end of treatment at Day 42
- Drug X, administered daily, Drug Y administered twice daily, including 1-week titration period followed by a 5-week flexible dose period
- Subjects must be hospitalized for an acute episode of schizophrenia
- After the enrollment visit and screening period of up to 7 days, the patient will be randomized on Day 1 to one of two treatments groups
- Subjects must remain inpatients for at least 14 days immediately after randomization

What are potential critical to quality aspects of this trial?

- Differences in hospitalization patterns across trial sites impacting recruitment and leading to early withdrawals post-randomization
- Not as likely to be hospitalized for acute episode in certain countries; challenge for recruitment
- In Spain, those aged 26–45 years had a shorter stay (17.6 days) than younger (29.9 days) or older (24.6 days) groups, potentially resulting in differential exclusion in sites in Spain


Salvador Peiró · Gregorio Gómez · Montserrat Navarro · Iris Guadarrama · Javier Rejas for the Psychosp group*

Length of stay and antipsychotic treatment costs of patients with acute psychosis admitted to hospital in Spain. Description and associated factors. The Psychosp study.


European Psychiatry

Volume 26, Issue 1, Supplement 1, March 2011, Pages 17-28

Country differences in patient characteristics and treatment in schizophrenia: data from a physician-based survey in Europe

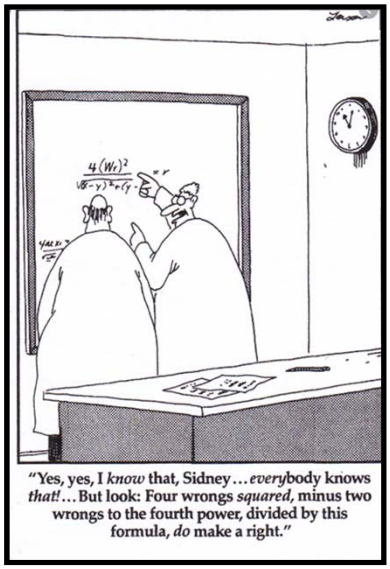
G. Papageorgiou [a] [A] [✉], F. Cañas [b], M. Zink [c], A. Rossi [d]

Potential mitigation strategies

- Quality Risk Management (QRM)
- Modify eligibility criteria related hospitalization and/or hospital length of stay
- Plan ahead for recruitment challenges; consider modifying the involved countries if the protocol is not amendable

Are we there yet?

- Despite resources devoted by sponsors to overseeing their trials, we still see cases in which trial conduct by investigators so deficient that data generated are not reliable and cases in which systemic error, whether occurring at site or in sponsor/CRO processes bring the integrity of an entire trial into question.
- Moreover, the types of regulatory violations observed in the clinical trial arena have remained static over time



"Yes, yes, I *know* that, Sidney … *every*body knows *that!*… But look: Four wrongs *squared*, minus two wrongs to the fourth power, divided by this formula, *do* make a right."

"The Far Side" by Gary Larson

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.

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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

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Barriers to implementation

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> 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."

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Ongoing "GCP Renovation" Incorporates QbD Concepts into ICH E8

One Proposed Approach to GCP Renovation

FDA

- Update ICH guidelines to both address study quality and provide further flexibility to address the increasing diversity of clinical trial designs and data sources now employed to support regulatory and other health policy decisions
- Modernize *ICH E8 General Considerations for Clinical Trials*
  - Review issues and questions most critical to study quality, e.g., "critical to quality" factors to be considered
  - Provide more comprehensive cross-reference to other ICH GLs with relevant discussions
- Further renovate *ICH E6 Good Clinical Practices* to address a broader range of study types.
  - Create umbrella document of key principles with subsidiary use cases/annexes addressing specific types of studies/ data sources

Presentation by Theresa Mullin ICH-DIA Forum November 12, 2016

Rules-based → Risk-based → Principles-based

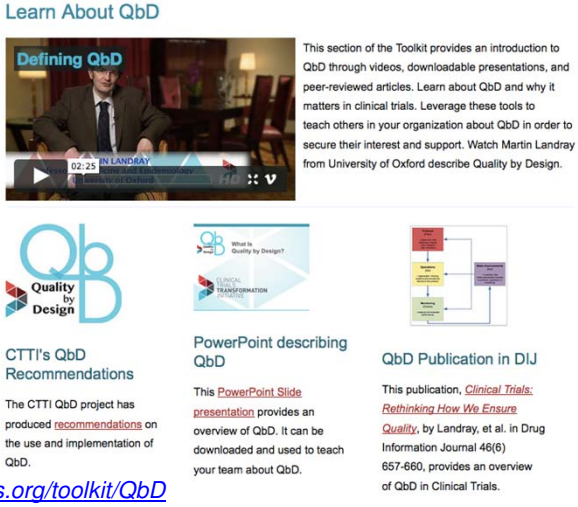
Clinical Studies / Data Sources:

1. Randomized Controlled Trial (current focus)
2. Adaptive Design Trials
3. Pragmatic clinical trials
4. Patient Registries
5. Virtual or Decentralized Trials
6. Randomized Controlled Trial with Real World Evidence Arm
7. Real World Evidence only (analyses of health care claim administrative data / electronic medical records)

CTTI QbD Toolkit

http://www.ctti-clinicaltrials.org/toolkit/QbD

Learn About QbD



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Introduce QbD

Introduce QbD to Your Team

QbD is about prospectively examining the objectives of a clicinal trial and defining those factors that are critical to meeting those objectives. This requires thinking differently about clinical trials. In order to do that effectively, we have provided tools below to help introduce your team to QbD concepts and how they apply in clinical trials. The sections include: understanding QbD; exploring critical to quality factors (CTQs) through the QbD Principles Document; and applying QbD through workshop tools.

Understanding QbD?

For this component, reference the earlier section in the Toolkit on Learn about QbD. You can also review CTTI's QbD Recmmendations.

QbD Principles Document

The Principles Document can be used to promote proactive, cross-functional discussions and critical thinking at the time of trial development about what is critical to quality for a specific trial, and about the events that might impede or facilitate achieving quality.

Workshop Tools

Hold a workshop to educate attendees about QbD and how to apply the QbD principles through hands-on exercises during breakout sessions. Case studies, facilitator tips, and presentation slide templates are provided. You can also leverage the past CTTI QbD workshop materials.

http://www.ctti-clinicaltrials.org/toolkit/QbD

Introduce QbD

Workshop Tools

Tools for hosting a QbD workshop within your own organization are provided. This includes case studies and a facilitation guide to educate attendees about clinical QbD and how to apply the QbD principles through hands-on exercises during breakout sessions. In addition, PowerPoint slide decks are provided as templates to build your own workshop. Past CTTI QbD workshop materials also are good resources.

Model Agenda for a QbD Workshop

CTTI's QbD Workshop Template Deck

QbD Workshop Facilitator Tips

http://www.ctti-clinicaltrials.org/toolkit/QbD

Adopting QbD

http://www.ctti-clinicaltrials.org/toolkit/QbD

Resources on the Web

- CTTI website → What We Do → QbD
  - Project overview
  - Recommendations
  - Webinars
  - Publications
  - Presentations
  - Principles Document
- QbD Toolkit
- Stay tuned for new materials!

Thank You

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Clinical Trials Transformation Initiative

Approach to Quality by Design

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CTTI Activities

Quality	Patient Engagement	Investigators & Sites
Quality by Design Informing ICH E6 Renovation Diversity Analysis of ClinicalTrials.gov Recruitment Planning for Pregnancy Testing State of Clinical Trials Report Monitoring	Patient Groups & Clinical Trials Patient Engagement Collaborative	Investigator Community Investigator Qualification Site Metrics

Mobile Clinical Trials	Novel Clinical Trial Designs	Ethics & Human Research Protection
Novel Endpoints Mobile Technologies Decentralized Clinical Trials Engaging Patients and Sites	Pragmatic Trials Real-World Data Registry Trials Master Protocols Antibacterial Drug Development Large Simple Trials Using FDA Sentinel for Trials	Single IRB Data Monitoring Committees Informed Consent Safety Reporting

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Origins of QbD 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?

Origins of CTTI's Work on QbD

- Current approach to trial monitoring is not effective
- 10% INDs fail to recruit a patient population appropriate to the intended use
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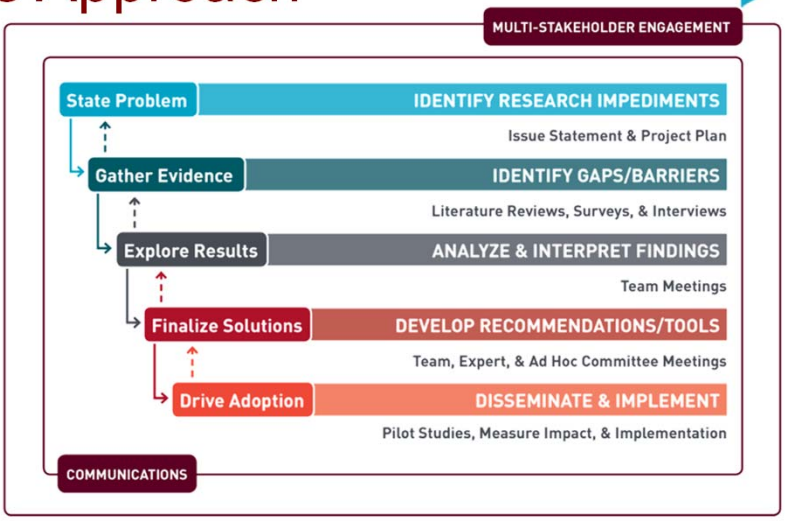

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CTTI's Approach

- Conduct projects to better understand the range of current practices, assess alternative approaches, understand barriers to change, and propose recommendations for improvement.

- Approach to transforming CT enterprise involves:
  - Engaging multiple stakeholders
  - Developing evidence-based, actionable recommendations
  - Improving clinical trials through implementation of CTTI recommendations and tools

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    - In addition, because new or unanticipated issues may arise once the study has begun, it is important to periodically review critical to quality factors to determine whether adjustments to risk control mechanisms are needed

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.

Principles Document: Key Concepts

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- Errors that have a meaningful impact on:
  - Patient safety or
  - Credibility of study results
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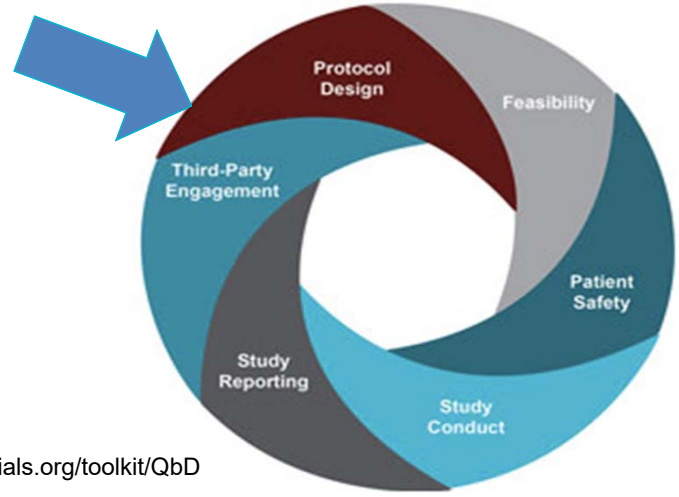
Exploring Critical to Quality Factors



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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?

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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

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?

Example: Data Monitoring & Management

CLINICAL TRIALS TRANSFORMATION INITIATIVE

Relative Importance

- Define critical data elements for data management during protocol development.
  - *(Are there data not critical for study analyses? Why collected?)*
- 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 *where relevant*

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?

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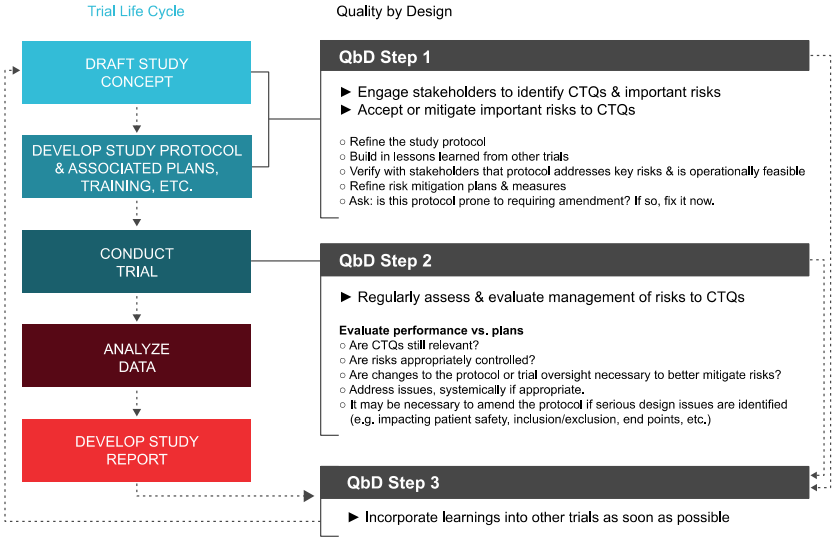
Application of **Quality by Design** in the trial life cycle

CTTI



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Real World Example

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Study Overview

- A 6-Week, multi-center, double-blind, double-dummy, active-controlled randomized study to evaluate the efficacy and safety of Drug X compared to Drug Y in the treatment of patients with acute episode of schizophrenia
- Phase III trial with 10 sites (US, UK, Germany, Spain)
- 250 patients, 1-year enrollment
- Primary outcome: Change from baseline of the Positive and Negative Syndrome Scale (PANSS) total score at the end of treatment at Day 42
- Drug X, administered daily, Drug Y administered twice daily, including 1-week titration period followed by a 5-week flexible dose period
- Subjects must be hospitalized for an acute episode of schizophrenia
- After the enrollment visit and screening period of up to 7 days, the patient will be randomized on Day 1 to one of two treatments groups
- Subjects must remain inpatients for at least 14 days immediately after randomization

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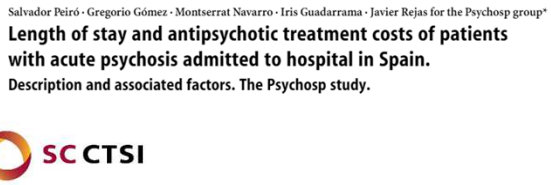
What are potential critical to quality aspects of this trial?

- Differences in hospitalization patterns across trial sites impacting recruitment and leading to early withdrawals post-randomization
- Not as likely to be hospitalized for acute episode in certain countries; challenge for recruitment
- In Spain, those aged 26–45 years had a shorter stay (17.6 days) than younger (29.9 days) or older (24.6 days) groups, potentially resulting in differential exclusion in sites in Spain


Salvador Peiró · Gregorio Gómez · Montserrat Navarro · Iris Guadarrama · Javier Rejas for the Psychosp group*

Length of stay and antipsychotic treatment costs of patients with acute psychosis admitted to hospital in Spain.
Description and associated factors. The Psychosp study.


European Psychiatry
Volume 26, Issue 1, Supplement 1, March 2011, Pages 17-28

Country differences in patient characteristics and treatment in schizophrenia: data from a physician-based survey in Europe

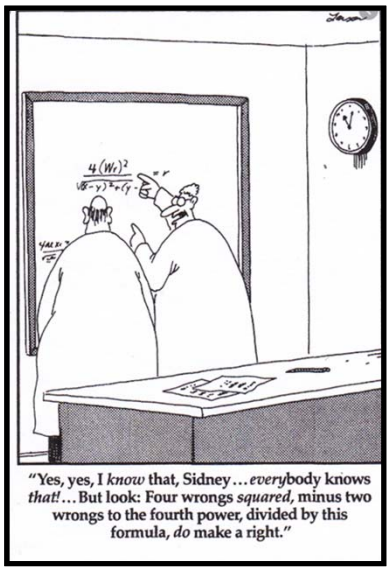
G. Papageorgiou [a] [A] [✉], F. Cañas [b], M. Zink [c], A. Rossi [d]

Potential mitigation strategies

- Quality Risk Management (QRM)
- Modify eligibility criteria related hospitalization and/or hospital length of stay
- Plan ahead for recruitment challenges; consider modifying the involved countries if the protocol is not amendable

Are we there yet?

- Despite resources devoted by sponsors to overseeing their trials, we still see cases in which trial conduct by investigators so deficient that data generated are not reliable and cases in which systemic error, whether occurring at site or in sponsor/CRO processes bring the integrity of an entire trial into question.
- Moreover, the types of regulatory violations observed in the clinical trial arena have remained static over time



"The Far Side" by Gary Larson

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One Key Challenge

CLINICAL TRIALS TRANSFORMATION INITIATIVE

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.

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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

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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."

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Ongoing "GCP Renovation" Incorporates QbD Concepts into ICH E8

One Proposed Approach to GCP Renovation

- Update ICH guidelines to both address study quality and provide further flexibility to address the increasing diversity of clinical trial designs and data sources now employed to support regulatory and other health policy decisions
- Modernize *ICH E8 General Considerations for Clinical Trials*
  - Review issues and questions most critical to study quality, e.g., "critical to quality" factors to be considered
  - Provide more comprehensive cross-reference to other ICH GLs with relevant discussions
- Further renovate *ICH E6 Good Clinical Practices* to address a broader range of study types.
  - Create umbrella document of key principles with subsidiary use cases/annexes addressing specific types of studies/ data sources

Presentation by Theresa Mullin ICH-DIA Forum November 12, 2016

Rules-based → Risk-based → Principles-based

Clinical Studies / Data Sources:

1. Randomized Controlled Trial (current focus)
2. Adaptive Design Trials
3. Pragmatic clinical trials
4. Patient Registries
5. Virtual or Decentralized Trials
6. Randomized Controlled Trial with Real World Evidence Arm
7. Real World Evidence only (analyses of health care claim administrative data / electronic medical records)

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CTTI QbD Toolkit

CLINICAL TRIALS TRANSFORMATION INITIATIVE

http://www.ctti-clinicaltrials.org/toolkit/QbD

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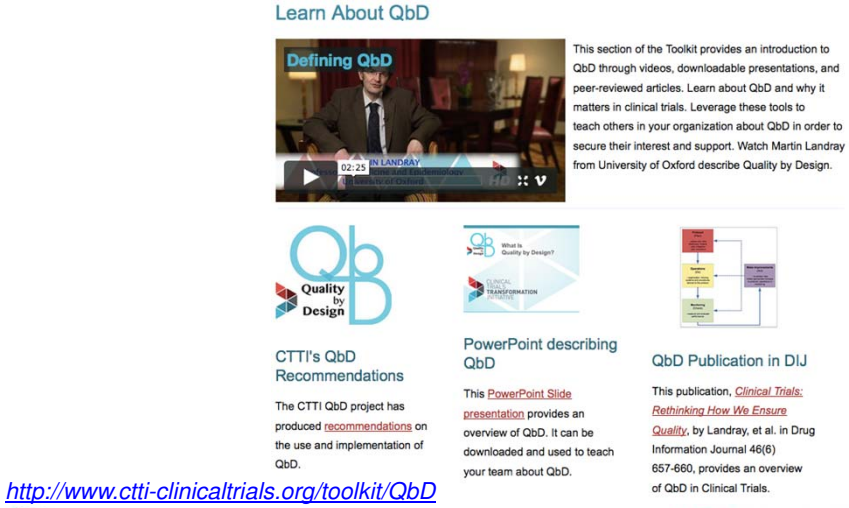
Learn About QbD

CLINICAL TRIALS TRANSFORMATION INITIATIVE



http://www.ctti-clinicaltrials.org/toolkit/QbD

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Introduce QbD

CLINICAL TRIALS TRANSFORMATION INITIATIVE

http://www.ctti-clinicaltrials.org/toolkit/QbD

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Introduce QbD

CLINICAL TRIALS TRANSFORMATION INITIATIVE

Workshop Tools

Tools for hosting a QbD workshop within your own organization are provided. This includes case studies and a facilitation guide to educate attendees about clinical QbD and how to apply the QbD principles through hands-on exercises during breakout sessions. In addition, PowerPoint slide decks are provided as templates to build your own workshop. Past CTTI QbD workshop materials also are good resources.

Model Agenda for a QbD Workshop

CTTI's QbD Workshop Template Deck

QbD Workshop Facilitator Tips

http://www.ctti-clinicaltrials.org/toolkit/QbD

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Adopting QbD

CLINICAL TRIALS TRANSFORMATION INITIATIVE

Adopt QbD

Understanding QbD is just the beginning. The real impact will occur when QbD is implemented at your organization as part of your fundamental approach to clinical trial design and operationalization. To support you in the work of adopting QbD, we have provided guidance to get started, introduce QbD to your team, and implement QbD. Watch as Coleen Glessner shares her insights on the benefits of thinking differently with QbD.

Get Started

This section provides insights for getting started and securing buy in within your organization.

Introduce QbD to Your Team

Leverage our tools provided in the sections: Learn about QbD and Introduce QbD to begin QbD discussions within your organization.

Implement

Adopting QbD take time and effort. In this section, we share tips and insights from others that have implemented QbD to help you in the process.

http://www.ctti-clinicaltrials.org/toolkit/QbD

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Resources on the Web

- CTTI website → What We Do → QbD
  - Project overview
  - Recommendations
  - Webinars
  - Publications
  - Presentations
  - Principles Document
- QbD Toolkit
- Stay tuned for new materials!

Thank You

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Implementation of Quality by Design (QbD) at Academic Health Centers

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Background

- A key part of the CTSA mission is embedding quality into clinical research at funded hubs and the global clinical research enterprise.
- What are the challenges facing the clinical trial enterprise?
- What are the available tools and mechanisms to leverage for this purpose?

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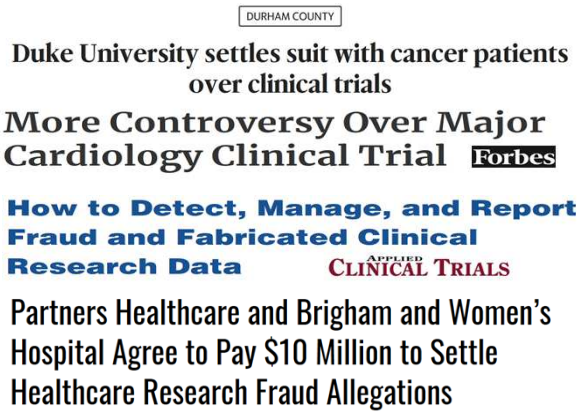
Challenge: Crisis of trust in clinical research

- The promise of translational research is to bridge the divide between preclinical discoveries and clinically relevant new therapies.
- Meaningful translation can only occur with clinical trials that are of **"quality"** i.e. address salient health challenges, efficiently generate accurate evidence, minimize participant risk, and engage all stakeholders.
- Unfortunately, the clinical trial enterprise has fallen short in achieving these goals leading to a crisis of public trust in biomedical research as well as inadequate translation of discoveries into effective therapies.



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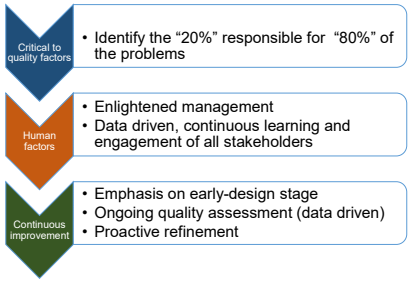
Solution: Quality by Design (QbD)

Background:

- Pioneering engineers, scientists, and statisticians in the mid 1900s [e.g., Joseph Juran and W. Edwards Deming] created systematic approaches to quality improvement.
- Rather than judging quality solely by examination of the end product, focus on key elements across the whole manufacturing process from start to finish.
- Three key principles of quality science include identification of critical to quality factors (CTQs) early in the design process, addressing human factors (training) and continuous improvement.
- Their "science of quality" was globally transformative.



Three key principles of quality science best practices as envisioned by Juran and Deming

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Solution: Quality by Design (QbD)

Embedding QbD into manufacturing

- The implementation of formalized quality science best practices is manifest today across many industries.
- More recently, QbD has been formally introduced to the pharma industry both in the US and globally.

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Solution: Quality by Design (QbD)

Theory to practice: embedding QbD and CTQ best practices into clinical research and trials

- Clinical Trials Transformation Initiative (CTTI), a public-private partnership co-founded by Duke University and the U.S. Food and Drug Administration (FDA), have pioneered efforts to develop and drive adoption of QbD into the clinical trial enterprise.
- Through a series of extensive multidisciplinary workshops, literature review, and critical evaluation, CTTI developed the concepts in QbD that can be applied to clinical research.

CTTI recommends that quality be built into the scientific and operational design and conduct of clinical trials ("quality by design") as follows:

1	Create a culture that values and rewards critical thinking and open dialogue about quality, and that goes beyond sole reliance on tools and checklists.
2	Focus effort on activities that are essential to the credibility of the study outcomes.
3	Involve the broad range of stakeholders in protocol development and discussions around study quality.
4	Prospectively identify and periodically review the critical to quality factors.

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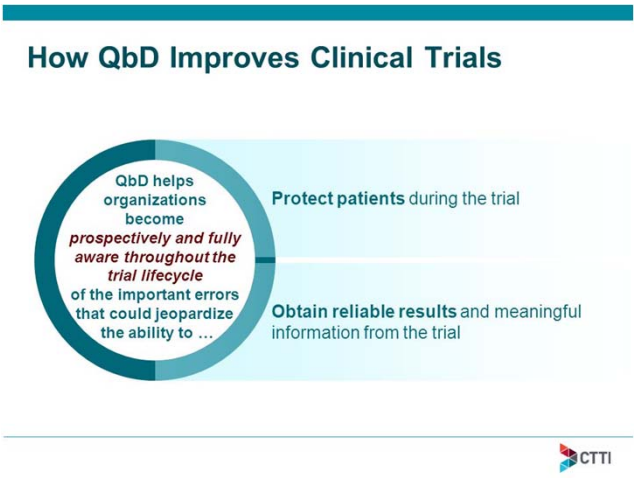
Solution: Quality by Design (QbD)

Theory to practice: embedding QbD and CTQ best practices into clinical research and trials

- Quality defined as “lack of errors that matter”
- Errors that can compromise integrity of trial (i.e. error in data collection or trial conduct) or compromise patient/participant safety
- This is done by focusing on critical to quality (CTQ) factors



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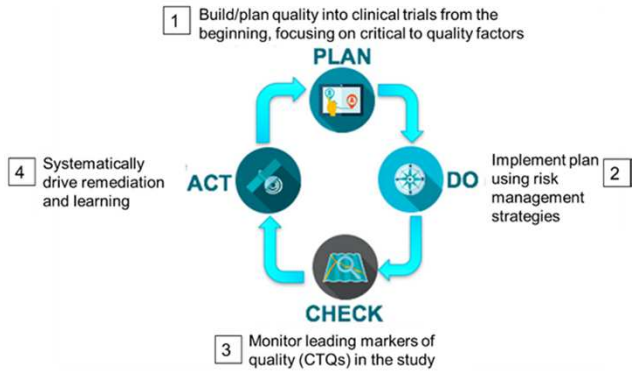
Solution: Quality by Design (QbD)

Critical to quality factors (CTQs) in clinical trials

- Understanding what is critical to quality allows for tailoring the protocol design to eliminate unnecessary complexity, avoid predictable errors in conduct as well as devising a focused and streamlined monitoring and auditing plan.
- To achieve this goal, CTTI developed a set of CTQs, documented in the CTQ Factors Principles Document (*).
- In the QbD approach, these crucial concepts are realized by prioritizing risk during study planning (plan), implementation of a risk-based approach to study conduct (do), review the study for errors that matter (check), and mitigating risk and incorporating learning in future studies (act).

* https://www.ctti-clinicaltrials.org/files/principles_document_finaldraft_19may15_1.pdf



QbD approach to planning, conduct and monitoring of clinical trials.

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Solution: Quality by Design (QbD)

Categories of CTQ factors* in clinical trials (developed by CTTI)

- Developed collaboratively by industry, regulators, and academia and were refined during a series of hands-on workshops involving over 200 attendees with a range of perspectives (including patient advocates, institutional review boards, academic trialists, clinical investigators, clinical research organizations, pharmaceutical and medical device companies, regulatory reviewers, and inspectors).
- Resources to support researchers in applying this approach to clinical trials, including formal Recommendations, an on-line QbD Toolkit, and Critical to Quality Factors Principles Document, among others.
- Additional resources to support adoption (e.g., metrics framework, maturity matrix, library of case studies) are currently in development by CTTI.

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CTQ: Categories

STUDY REPORTING	
Dissemination	Is it clear who has the right to prepare publications and reports using the study data?
THIRD PARTY ENGAGEMENT	
Sponsor responsibilities	How will potential conflicts between standard operating procedures of the sponsor and the third party be resolved?
Collaborations	What mechanisms are in place to ensure timely and appropriate access to information for all parties?
*CTTI developed 149 examples of CTQs for the categories listed in the Table	
Statistical analysis	Are there measures to ensure that study statisticians are aware of the clinical implications of study objectives and endpoints?

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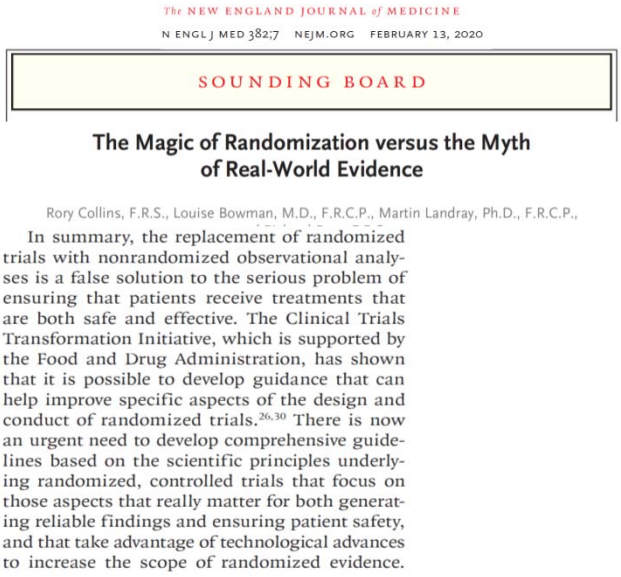
QbD an imperative

What's missing?

- The QbD approach has been well-described and detailed in publications, toolkits and workshops.
- A robust and validated implementation plan remains to be established.
- We contend that academic health centers (AHCs) would be the ideal setting for evaluating the adoption of QbD in clinical research.



The NEW ENGLAND JOURNAL of MEDICINE

N ENGL J MED 382;7 NEJM.ORG FEBRUARY 13, 2020

SOUNDING BOARD

The Magic of Randomization versus the Myth of Real-World Evidence

Rory Collins, F.R.S., Louise Bowman, M.D., F.R.C.P., Martin Landray, Ph.D., F.R.C.P.,

In summary, the replacement of randomized trials with nonrandomized observational analyses is a false solution to the serious problem of ensuring that patients receive treatments that are both safe and effective. The Clinical Trials Transformation Initiative, which is supported by the Food and Drug Administration, has shown that it is possible to develop guidance that can help improve specific aspects of the design and conduct of randomized trials.[26,30] There is now an urgent need to develop comprehensive guidelines based on the scientific principles underlying randomized, controlled trials that focus on those aspects that really matter for both generating reliable findings and ensuring patient safety, and that take advantage of technological advances to increase the scope of randomized evidence.

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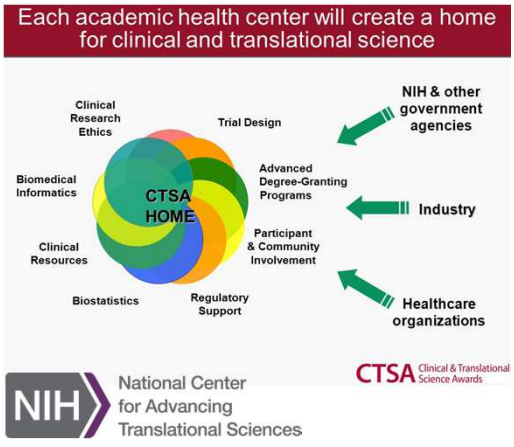
QbD Adoption: Academic Health Centers

Why AHCs and CTSAs?

- Association of American Medical colleges "Medical schools and teaching hospitals educate the next generation of physicians, conduct cutting-edge research that saves lives, and care for the sickest and most complex patients."
- The NIH has recognized the critical role played by AHCs in clinical research throughout all of its centers and institutes.
- In particular, the creation of the CTSAs followed by the inauguration of the National Center for Advancing Translational Sciences has catalyzed AHCs to lead the nation in rigorous, data-driven efforts to dramatically improve clinical research and the quality of clinical trials.



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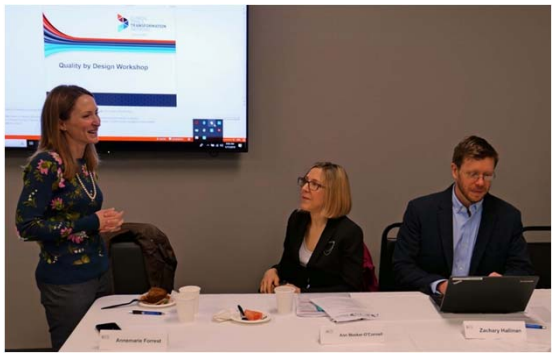
QbD at the local level: UC Irvine QbD Workshop

Workshop at UC Irvine
"Implementing QbD at an Academic Health Center"
CTTI's Annemarie Forrest, Ann Meeker-O'Connell, and Zach Hallinan open the event



Attendees included the Dean of School of Medicine, Associate Vice Chancellors for Research Administration and Research Engagement other leadership and key stakeholders involved in clinical research

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UC Irvine QbD Workshop

Evaluation of the Workshop

QbD approach and workshop was very well-received.

Table 2. Individual Learning Objective and Statement Ratings

Learning Objectives and Statements	% Disagree[1]	Neutral	% Agree[2]
After today's workshop, I feel that I have a good basic understanding of the QbD principles	0	5	95
I can imagine a pathway whereby QbD principles would be applied widely at UCI	0	5	95
I am interested in applying QbD processes to my own research.	0	6	94

[1]Combination of strongly disagree and somewhat disagree
[2]Combination of strongly agree and somewhat agree

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QbD at local level: Implementation of QbD at UC Irvine

- **Creation of QbD working group (QbD-WG)**
- **Mission of the working group-**
  - Support investigators toward the goal of enhancing the quality of clinical trials at UC Irvine by implementing QbD concepts. To that end, the working group will
    - be a resource to investigators for design and conduct of clinical trials.
    - will provide guidance regarding the pragmatic aspects of clinical trial implementation using the QbD approach including application of critical to quality (CTQ) principles to clinical trial design and management.

UC•IRVINE ICTS *from lab to life.*

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QbD at local level: Implementation of QbD at UC Irvine

- **QbD-Working Group composition-**
  - **Core members:** Expert in informatics, Expert in statistical design, Recruitment expert, Regulatory expert, Senior study coordinator/Research nurse, Experienced clinical trial investigators**.**
  - **Ad-Hoc members:** Individualized based on each study.
- **A 2-year pilot project**,
  - The goal will be to apply QbD principles over a 2-year period to selected clinical trials.
  - QbD team will meet with the PI and provide feedback/suggestions.
  - One study evaluated every 3 months.

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QbD at local level: Implementation of QbD at UC Irvine

- **Three studies reviewed so far-**
  - Neurosurgical implantation of therapy with a sham group
  - Dietary intervention in hematologic disorder
  - Prospective microbiome study
- **Learning Health System:**
  - Evaluation of each session used to improve future meetings.
  - KL2 and TL awardees invited to the working group meetings to increase familiarity with QbD approach and enhance its adoption.

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QbD at national level: Bigger picture for QbD implementation

CTSA Collaborative Innovation Award

- A multicenter, multi-stakeholder project to
  - A) Create a formalized pathway for adoption of QbD
  - B) Come up with initial metrics to evaluate the potential impact of QbD on clinical research quality
  - C) Establish a sustainability and dissemination plan
- As such, this project brings together a diverse group of institutions with the experience and expertise needed to evaluate novel ways of embedding the concept of "Quality-by-Design (QbD)" in clinical research conducted at AHCs.
- Participating institutions UC Irvine, Kansas University, Dartmouth & Georgetown/Howard CTSA hubs, Brown University (IDeA), CTTI with consultation from TIN.

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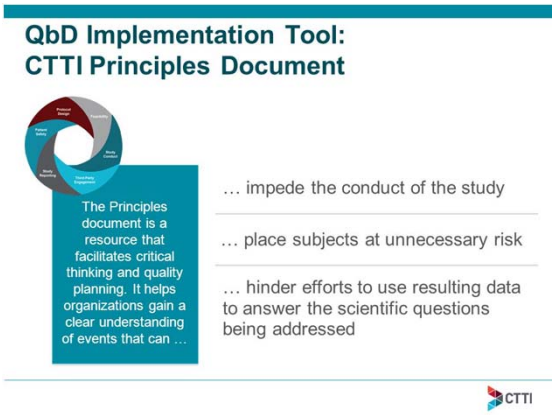
QbD at national level: Bigger picture for QbD implementation

CTSA Collaborative Innovation Award

- The goal of this project is to synergize two distinct interventions:
  - 1) training of clinical trial personnel in the concept model of QbD (as created at Kansas University)
  - 2) workshops focused on individual clinical trials in which QbD is built into studies at the earliest phases of clinical trial development (as established at UC Irvine).
- In both interventions, the key QbD process is finding and prioritizing the "critical to quality" factors or elements (CTQs), defined as "aspects of a trial essential to generating reliable data and providing appropriate protection of research participants."



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Bigger picture for QbD implementation

CTSA Collaborative Innovation Award

- We propose a multipronged, multisite intervention with a robust implementation plan and well-defined metrics.

Specific Aims:

- **1. Embed QbD-training into institutional support for research.** This aim will be accomplished by creating a formal training program (learning module [LM]) at each hub for clinical trial principal investigators and key staff with an emphasis on the concept of critical-to-quality factors (**CTQ-LM**). The training approach emphasizes overall concepts used to define, identify, and prioritize CTQs.
- Hypothesis: A CTQ-LM directed at key study personnel will result in increased identification and prioritization of CTQ factors.
- Preliminary data - Kansas University

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Bigger picture for QbD implementation

CTSA Collaborative Innovation Award

Specific Aims:

- **2. Introduce CTQ Working Group (CTQ-WG) for individual clinical trials at early stages of study development.** Building on aim 1, this aim will be accomplished by formation of CTQ-WG at each hub that work with individual clinical trial teams to define, identify, and prioritize CTQs.
- Hypothesis: A CTQ directed design studio (CTQ-WG) targeting individual clinical trial teams will alter and improve the team's subsequent study design and development.
- Preliminary data from UC Irvine

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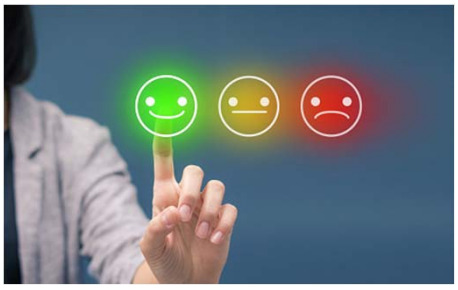
Bigger picture for QbD implementation

CTSA Collaborative Innovation Award

Specific Aims:

- **3. Measure the impact of QbD adoption via CTQ-LM and CTQ-DS on clinical trials recruitment and retention and participant experience/satisfaction.** This aim will be accomplished by randomizing pilot projects at each hub to either the QbD adoption program or conventional hub practices. Subsequently, metrics related to trial efficiency (recruitment and retention) and participant satisfaction will be evaluated.
- Hypothesis: A CTQ-focused implementation program will result in improved clinical trial efficiency and enhanced participant and investigator satisfaction.



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Articles

Research Participant-Centered Outcomes at NIH-Supported Clinical Research Centers

Rhonda G. Kost, M.D.[1], Laura N. Lee, B.S.N., M.S.[2], Jennifer L. Yessis, Ph.D.[3], Robert Wesley, Ph.D.[2], Sandra Alfano, Pharm.D.[4], Steven R. Alexander, M.D.[5], Sylvia Baedorf Kassis, M.P.H.[6], Philip Cola, M.A.[7], Ann Dozier, R.N., Ph.D.[8], Dan E. Ford, M.D., M.P.H.[9], Paul A. Harris, Ph.D.[10], Emmelyn Kim, M.A., M.P.H.[11], Simon Craddock Lee, Ph.D., M.P.H.[12], Gerri O'Riordan, R.N.[5], Mary-Tara Roth, R.N., M.S.N., M.P.H.[6], Kathryn Schuff, M.D.[13], June Wasser, M.A.[14], David K. Henderson, M.D.[2], and Barry S. Coller, M.D.[1]

Abstract

Background: Although research participation is essential for clinical investigation, few quantitative outcome measures exist to assess participants' experiences. To address this, we developed and deployed a survey at 15 NIH-supported clinical research centers to assess participant-centered outcomes; we report responses from 4,961 participants.

Methods: Survey questions addressed core aspects of the research participants' experience, including their overall rating, motivation, trust, and informed consent. We describe participant characteristics, responses to individual questions, and correlations among responses.

Results: Respondents broadly represented the research population in sex, race, and ethnicity. Seventy-three percent awarded top ratings to their overall research experience and 94% reported no pressure to enroll. Top ratings correlated with feeling treated with respect, listened to, and having access to the research team ($R^2 = 0.80–0.96$). White participants trusted researchers more (88%) than did nonwhite participants collectively (80%; $p < 0.0001$). Many participants felt fully prepared by the informed consent process (67%) and wanted to receive research results (72%).

Conclusions: Our survey demonstrates that a majority of participants at NIH-supported clinical research centers rate their research experience very positively and that participant-centered outcome measures identify actionable items for improvement of participant's experiences, research protections, and the conduct of clinical investigation. Clin Trans Sci 2014; Volume 7: 430–440

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Bigger picture for QbD implementation

CTSA Collaborative Innovation Award

Expected Outcomes/Impact

- The proposed study will
- 1) establish a new collaboration between three CTSAs and one CTR to help address a translational science problem that no one hub can solve alone
- 2) establish a system to allow solutions that have been developed at each hub to be adopted and implemented across other organizations, thereby testing their robustness to different hub environments and adapting them for further dissemination within and outside the CTSA program consortium
- 3) provide a platform for evaluating the role of the QbD approach in addressing the issue of quality in clinical trials.

UNIVERSITY OF CALIFORNIA · IRVINE · LET THERE BE LIGHT

CLINICAL TRIALS TRANSFORMATION INITIATIVE

KU THE UNIVERSITY OF KANSAS

BROWN

DARTMOUTH 1769 VOX CLAMANTIS IN DESERTO

GEORGETOWN UNIVERSITY

TRIAL INNOVATION NETWORK

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Bigger picture for QbD implementation

CTSA Collaborative Innovation Award

- 4) these efforts will help develop and examine metrics which can be measured and are highly relevant to the concept of quality in clinical trials.
- 5) the pathways, infrastructures and solutions developed as part of this proposal can then be used as a platform to disseminate QbD at other institutions.

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USC RegSci | https://regulatory.usc.edu/	Phone: (323) 442-3521	Email: regsci@gmail.com	Insta: @RegSci

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Integrating Quality by Design, Team Science, and Project Management for Research Success

Allison Orechwa, PhD
Director of Programmatic Development
Southern California Clinical and Translational Science Institute (SC CTSI)

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The Need

CLINICAL TRIALS TRANSFORMATION INITIATIVE

- 10% INDs fail to recruit a patient population appropriate to the intended use
- 3% of NDAs not approved due to missing critical data
- 25% of study procedures in phase 3 trials are not relevant to the assessment of primary endpoints
- Completed protocols across all phases average 2-3 amendments, 1/3 avoidable, all expensive
- USC and CHLA: Only 45% of trials reach their enrollment targets

DiMasi JA. *Cost of developing a new drug*, http:// csdd.tufts.edu/files/uploads/Tufts_CSDD_briefing_on_RD_cost_study_ Nov_18,_2014.pdf.

Getz KA, Stergiopoulos S, Marlborough M, et al. Quan- tifying the magnitude and cost of collecting extraneous protocol data. *Am J Ther* 2015; 22: 117–124.

http://csdd.tufts.edu/files/uploads/Summary-JanFebIR2016_.pdf

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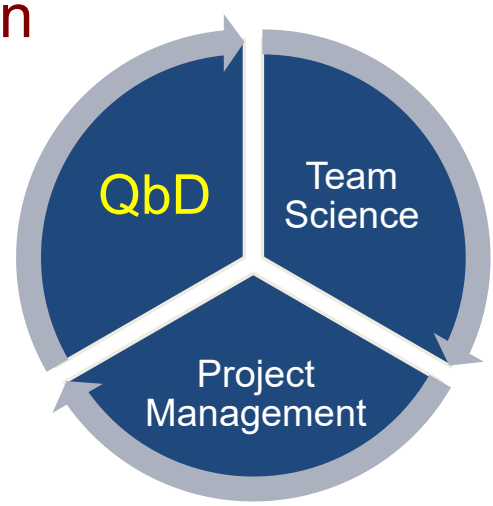
The USC Solution



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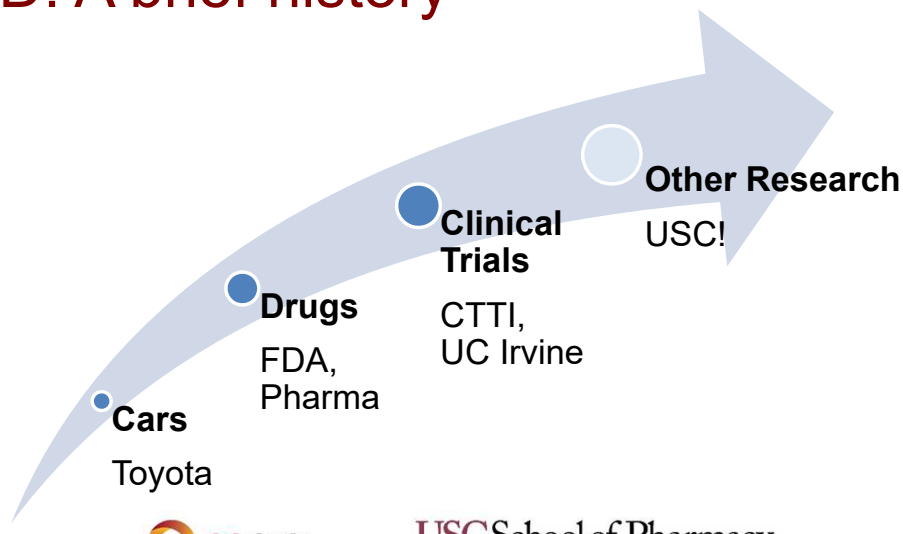
QbD: A brief history



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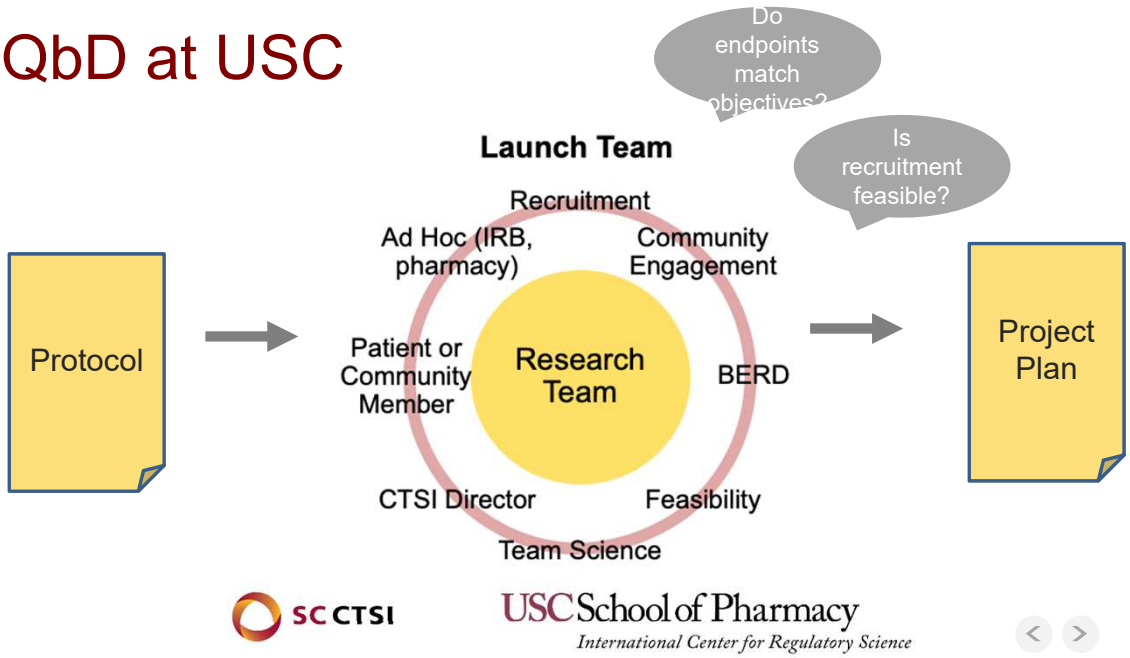
Discussion Categories	For Clinical Trials (Drugs & Devices)	For Clinical Trials (Behavioral)	For non-Clinical Trials (outcome, biomarkers, diagnostics etc. research)
Protocol Design	Eligibility Criteria	Eligibility Criteria	Eligibility Criteria
	Randomization	Randomization	
	Masking	~~Masking~~	~~Masking~~
	Types of Controls	Types of Controls	~~Type of Controls~~
	Data Quantity	Data Quantity	Data Availability & Quantity
	Endpoints	Endpoints	Endpoints
	Procedures Supporting Study Endpoints and Data Integrity	Procedures Supporting Study Endpoints and Data Integrity, e.g., surveys	Procedures Supporting Study Endpoints and Data Integrity
	Investigational Product Handling and Administration	~~Investigational Product Handling and Administration~~	~~Investigational Product Handling and Administration~~
		Integrity of Intervention Delivery (training, monitoring)	?
Feasibility	Study and Site Feasibility	Study and Recruitment Site Feasibility	Study and Recruitment Site Feasibility
	Accrual	Accrual	Accrual
Patient Safety	Informed Consent	Informed Consent	Informed Consent
	Withdrawal Criteria and Trial Participant Retention	Withdrawal Criteria and Trial Participant Retention	Withdrawal Criteria and Participant Retention
	Signal Detection and Safety Reporting	Safety Reporting	
	Data Monitoring Committee/Stopping Rules		
Study Conduct	Training	Training	Training
	Data Recording and Reporting	Data Recording and Reporting	Data Recording and Reporting
	Data Monitoring and Management	Data Monitoring and Management	Data Monitoring and Management
	Statistical Analysis	Statistical Analysis	Statistical Analysis
Study Reporting	Dissemination of Study Results	Dissemination of Study Results	Dissemination of Study Results
Third-Party Engagement	Delegation of Sponsor Responsibilities	~~Delegation of Sponsor Responsibilities~~	~~Delegation of Sponsor Responsibilities~~
	Collaborations	Collaborations	Collaborations

QbD at USC



QbD Resources

- Training
- Adapted Principles Documents
- Templates: Launch Meeting Checklist, Project Management Plan
- Consultations

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Exercise

Different factors will stand out as critical for different types of trials.

1. Imagine one of your own studies.
2. Select the highest priority Critical to Quality Factor.
3. Consider the following:
   - What are the risks related to this factor?
   - 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?

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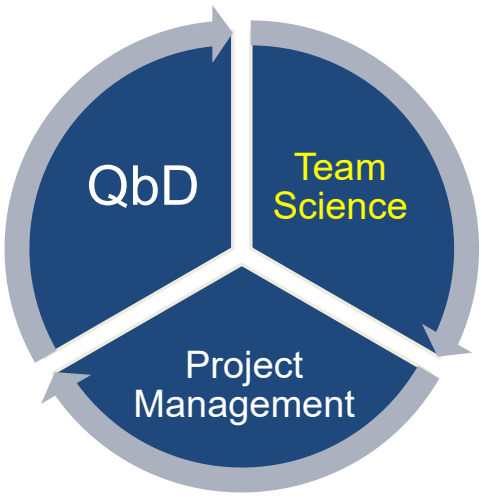
The USC Solution



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Team Science

"Collaborations among researchers and across disciplinary, organizational, and cultural boundaries are vital to address increasingly complex challenges and opportunities in science and society."

Boundary-spanning teams have greater productivity and scientific impact.

Hall KL, Vogel Amanda L, Huang GC, Serrano KJ, Rice EL, Tsakraklides SP, Fiore SM. *The science of team science: A review of the empirical evidence and research gaps on collaboration in science.* American Psychologist, Vol 73(4), May-Jun 2018, 532-548

"My research now includes a focus on the perception and behaviors of the Latino community with MS to better understand how they live with disabilities that come with the disease."

CTSA Program Community Mentorship Helps Advance Multiple Sclerosis Research in Latinos.
https://ncats.nih.gov/pubs/features/usc-ms

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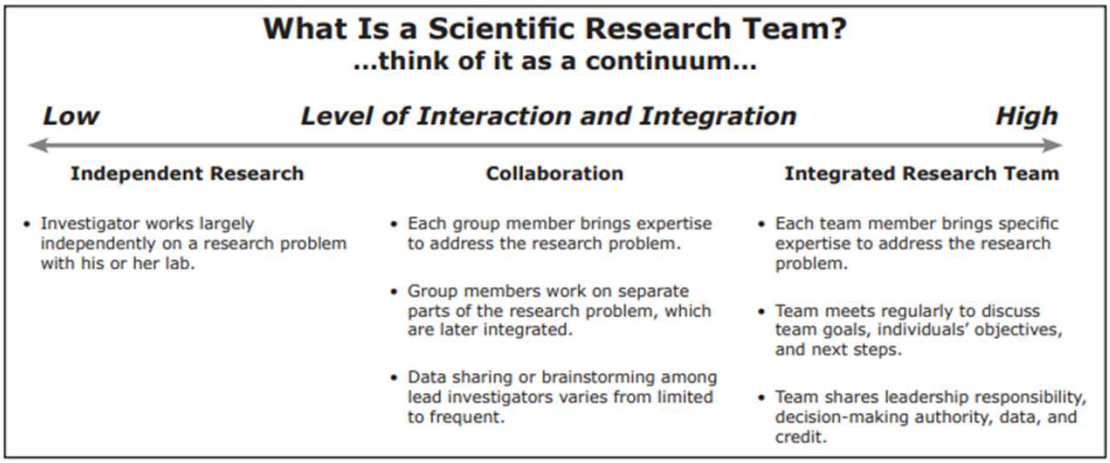
Team Science



Collaboration and Team Science Field Guide By Bennett, Gadlin, and Marchand National Institutes of Health. 2018

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Team Science

1. **Develop a shared vision**
   - Agree on how to achieve the vision
   - Set clear and tangible short- and long-term goals together
   - Establish responsibilities in writing (MOU)
2. **Communicate**
   - Decide how you will communicate (frequency, platform)
   - Set ground rules
   - Support contribution by all team members
   - Listen
   - Accept that conflict and disagreement are normal
3. **Agree on deliverables**
   - Determine output of the team
   - Decide on milestones and timeline
   - Develop an expectation that data and results will be shared with all members

Tip: *SC CTSI Team Building Grant provides rapid funding for activities that promote the assembly of new multidisciplinary or transdisciplinary teams.*

SC CTSI Research Development "Before You Start" Guide.
https://sc-ctsi.org/training-education/building-effective-collaborations

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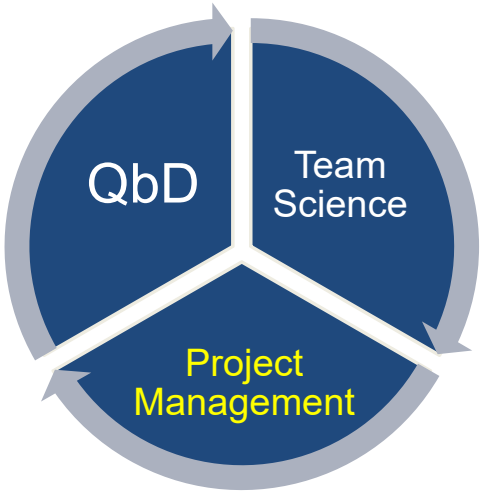
The USC Solution



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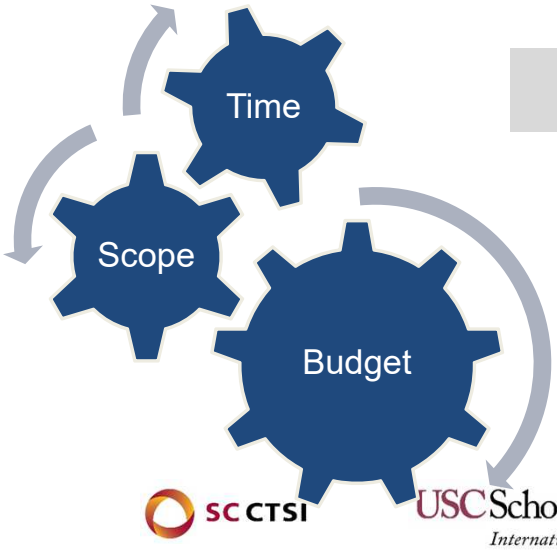
Project Management Essentials



"Goals are dreams with deadlines."
~Diana Scharf

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Project Management Essentials

Foundation

People + Process = Success

Initiate

Clarify a shared and measurable set of expectations

Plan

Create a clear road map for smart decision making

Execute

Engage people through consistent and shared accountability

Monitor & Control

Drive progress through transparent communication

Close

Measure success and get better

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Project Planning: Accrual Projections

Stage	Worst Case	Best Case	Actual
Pre-Screening	80	120	90
Screening	50	100	60
Randomization	25	60	40
Follow-Up	10	45	10

What is the issue? Was it avoidable?

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Appendix

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CTQ Example

PROTOCOL DESIGN			
Factor	**Description/Rationale**	**Potential Considerations in Evaluating Relative Importance of CTQ Factor**	**Examples of Issues to Consider in Evaluating Risks to CTQ Factor**
Eligibility Criteria	Carefully designed eligibility criteria ensure that the intended study population is enrolled and that trial participants for whom participation may be harmful are not included. Ambiguity may result in inconsistent application across sites; overly restrictive criteria may limit the real-world applicability of results or impede trial participant recruitment. Each criterion should be evaluated in terms of its utility in 1) defining the population, 2) excluding trial participants for whom there are safety concerns, 3) avoidance of confounding of efficacy measures, and 4) identifying contraindicated medications or procedures. If the criterion does not have utility by these measures, the rationale for retaining it should be further considered.	1. Describe the specific population needed for the trial to evaluate the intended question. If this specific population is not enrolled, will trial results be brought into question? 2. Are there trial participant populations that must be excluded from enrollment due to specific safety concerns with administration of the product to that population? 3. Evaluate the impact of "getting it wrong" with regard to eligibility. If a trial participant is found to not meet a criterion, what is the impact on the trial? 4. Is the trial intended to evaluate effectiveness and safety of the investigational product in a real-world population that would be likely to receive the product after approval? 5. What are the commonly accepted criteria for diagnosing and evaluating patients: a. With the disease under study? b. With comorbid conditions that are exclusionary? 6. Have PPAO and participating investigators provided imput as to the feasibility of implementing criteria?	1. Are all criteria relevant to ensuring the specific trial participant population needed for the trial? 2. Are additional steps necessary to balance population or ensure subsets (e.g., minorities) are sufficiently enrolled? 3. Are there clear and measureable criteria to define the population (e.g., "atrial fibrillation" or "diabetes")? 4. Is there a particular criterion critical to trial participant evaluability (e.g., for an enrichment design) or to trial participant safety (e.g., contraindicated medications or procedures)? Who generates/reports data on whether a trial participant meets this criterion? 5. Does the protocol elaborate on the desired trial participant population and/or the potential risks of participation, and are these statements reflected in the eligibility criteria? 6. What are the considerations with regard to timing of eligibility review vs. enrollment/randomization/ treatment? 7. Do any eligibility criteria require involvement of third parties external to the clinical site? What measures will ensure that information is submitted and/or received in a timely manner to permit enrollment?

Design for Six Sigma (DFSS)

Applying Design for Six Sigma

Nick Vyas Ed.D.
Data Sciences and Operations
USC, Marshall School of Business

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DESIGN FOR SIX SIGMA (DFSS)

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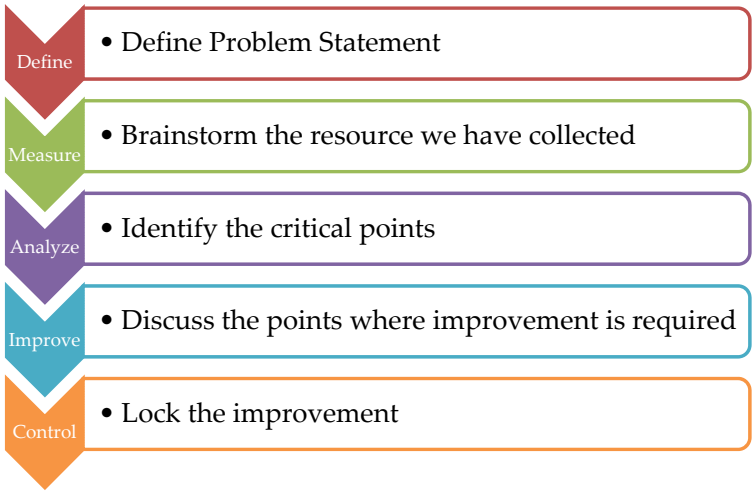
The Improvement Journey



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Improve Phase Objectives

- Let's abandon assumptions and consider all possible solutions
- Think outside of the box but stay with the project scope box
- Look to integrate future state that strikes the balances cost/service/speed/quality and control
- Understand best practice for process workflow
- Develop pilot and define implementation strategies

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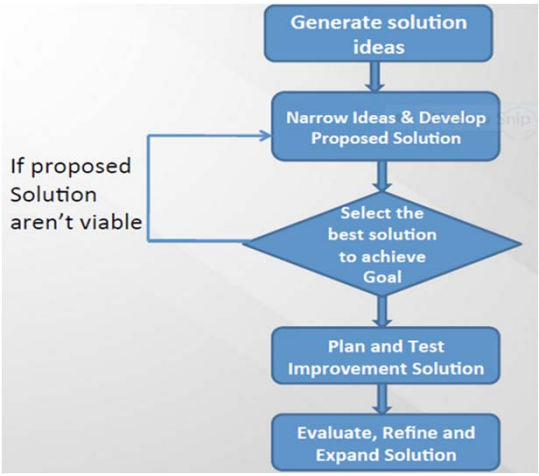
Improve Roadmap



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EVALUATING POTENTIAL SOLUTIONS

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Reasons for Experiments

- The Analyze Phase narrows down inputs to the critical few.
- It is necessary to determine the proper settings for vital inputs because:
  - potential interactions
  - have preferred ranges to achieve optimal results
  - Confirm cause and effect relationships among known factors

Reasons for Experiments

- Understanding the purpose of an experiment leads to ease in focusing the efforts of an experiment and determining design.

Reasons for experimenting are:

- Problem Solving: Improving a process response
- Optimizing: Highest yield or lowest customer complaints
- Robustness: Constant response time
- Screening: Further screening of the critical few to the vital few X's

Desired Results of Experiments

Problem Solving

- Eliminate defective products or services
- Reduce cycle time of handling transactional processes

Optimizing

- Mathematical model is desired to move the process response
- Opportunity to meet differing customer requirements (Specifications or VOC)

Desired Results of Experiments

Robust Design

- Provide consistent process or product performance
- Desensitize the output response(s) to input variable changes including NOISE variables
- Design processes knowing within input variables are difficult to maintain

Screening

- Past process data is limited or statistical conclusions prevented good narrowing of critical factors in the Analyze Phase

DESIGN OF EXPERIMENTS

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Definition: Design of Experiments

Design of Experiments (DOE)

- A scientific method of planning and conducting an experiment that will yield the true cause-and-effect relationship between the X/Y variables of interest

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Definition: Design of Experiments

DOE allows the experimenter to study …

- the effect of input variables that may influence the product or process **simultaneously**, as well as possible interaction effects.

Definition: Design of Experiments

Goal of DOE

- to find a design that will produce the information required at a minimum cost.
- Properly designed DOE's are more efficient experiments.

The end result of experiments describes results as a mathematical function

$$Y = f(x)$$

Design of Experiments (DOE)

Post-Pilot Priorities

- Assess and verify results
- Refine solution, adjust procedures as needed
- Review readiness for "full-scale" roll out
- Consider second pilot or other tests
- Revise/expand implementation plan
- Refine measures and monitoring – with an eye toward "Control"
- Prepare communication plan

Verifying Results

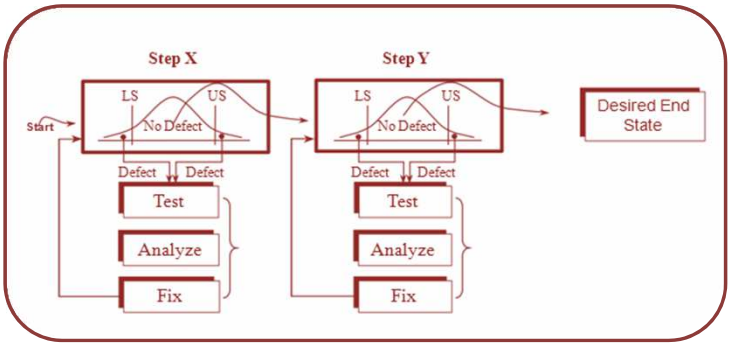
Evaluate change in performance vs. "baseline"

- Has goal (Project Y) been met, or is it trending to target?
- Is observed improvement clearly correlated to solution?
- Was efficiency sustainable?
- Were/are risks manageable?

Confirm/assess impact at "business" level

- Do "high level" measures & finances reflect results?
- Are gains offset by other costs?

How Process Capability Impacts Cycle Time and Resource Allocation



- Every Time a Defect is Created During a Process (Step), it Takes Additional Cycle Time to Test, Analyze, and Fix.
- These Non-Value Added Activities Typically Require Additional Floor Space, Capital Equipment, Material, and People

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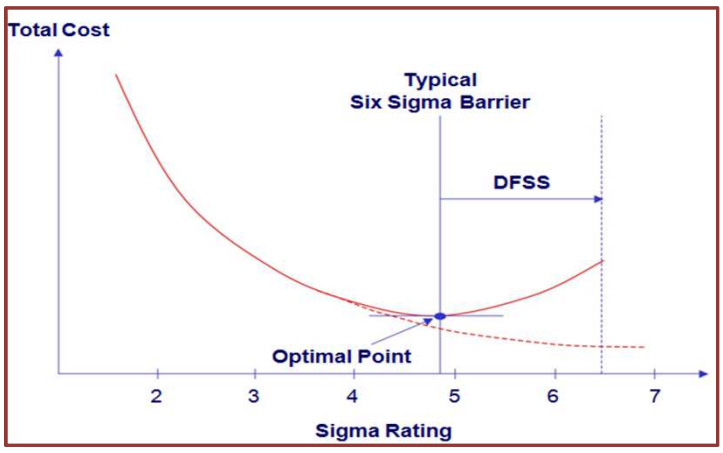
What Have We Learned From Six Sigma?



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DFSS – What is it?

Design for Six Sigma is:

- A methodology for designing new products and/or processes.
- A methodology for redesigning existing products and/or processes.
- A way to implement the Six Sigma methodology as early in the product or service life cycle as possible.
- A way to exceed customer expectations
- A strategy towards extraordinary ROI

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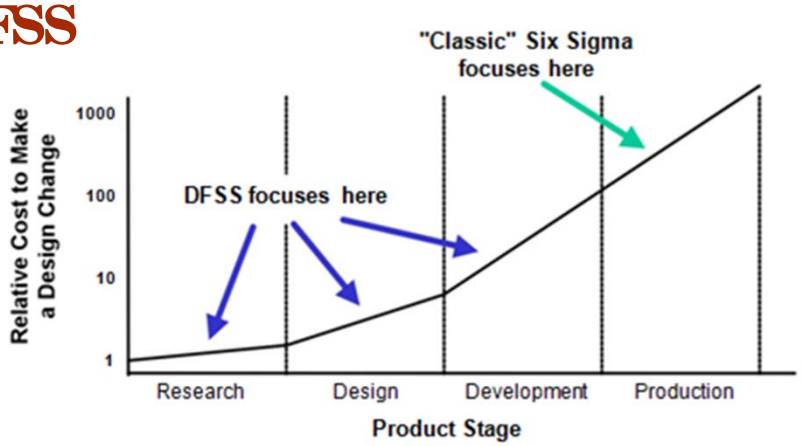
Why DFSS



- "Design in" quality when costs are lowest
- Show customers "Six Sigma" products right from the start

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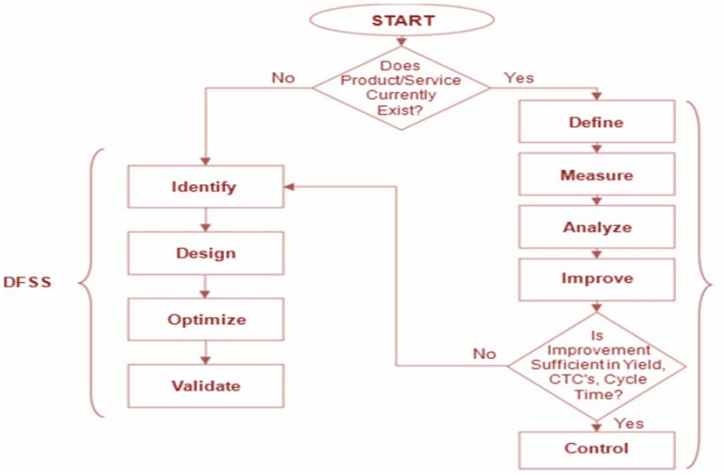
The Big Picture



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The Benefits of DFSS

- Goal: Create new game-changing products and services which:
  - Wow customers with 6s performance on their CTCs
  - Have 6s reliability
  - Have 6s manufacturability
  - Have high performance/cost ratios

- Payoffs:
  - Quality designed in from the start
  - Revenue growth: customer delight, market share, volume, price
  - Warranty cost reductions

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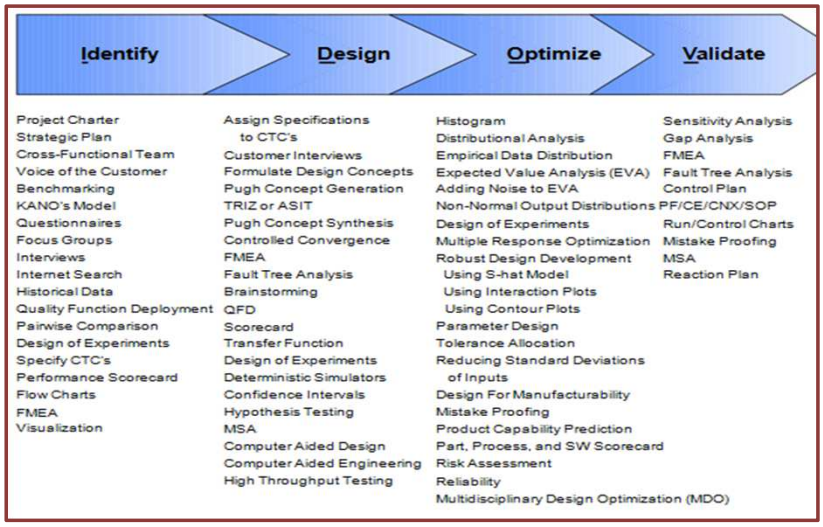
DFSS Tools



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TAGUCHI LOSS FUNCTION

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Taguchi Methods

- **Dr. Genichi Taguchi** is a Japanese statistician and Deming prize winner who pioneered techniques to improve quality through Robust Design of products and production processes.
- Dr. Taguchi developed fractional factorial experimental designs that use a very limited number of experimental runs.

Taguchi Methods

- The specifics of Taguchi experimental design is useful to understand Taguchi's Loss Function, which is the foundation of his quality improvement philosophy.
- Traditional thinking is that any part or product within specification is equally fit for use. In that case, loss (cost) from poor quality occurs only outside the specification

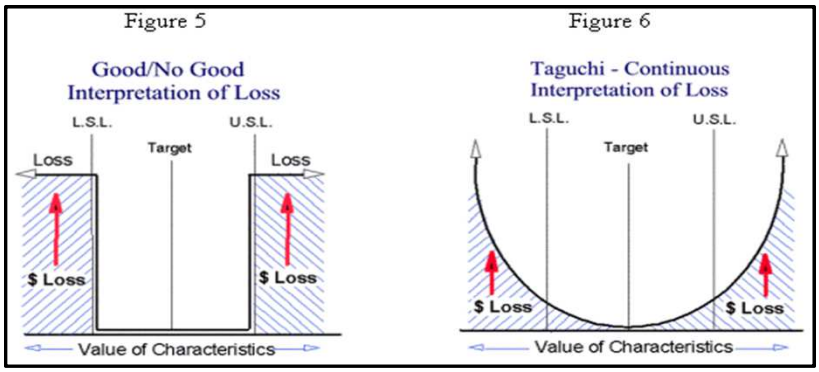
Taguchi Methods

- However, Taguchi makes the point that a part marginally within the specification is really little better than a part marginally outside the specification.
- As such, Taguchi describes a continuous Loss Function that increases as a part deviates from the target, or nominal value

Taguchi Methods

- The Loss Function stipulates that society's loss due to poorly performing products is proportional to the square of the deviation of the performance characteristic from its target value.

Taguchi Methods – Loss Function



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TOYOTA PRODUCTION SYSTEM (TPS)

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Toyota Production System

- https://www.youtube.com/watch?v=T5zcCk-uF3g
  - (longer video)
- https://www.youtube.com/watch?v=nFu4FFgbMY4
- https://www.youtube.com/watch?v=qcWEr2gh0Sg

Toyota Production System

- Production System developed by the Toyota Motor Corporation by Taiichi Ohno in the 1950s and 1960s in Japan
- Premise is to provide best quality, lowest cost, and shortest lead time through the elimination of waste within the process
- Pillars:
  - Just-In-Time Production
  - Jidoka

TPS Time Line

- 1930s: Concept of Just-In-Time (JIT) developed by Kiichiro Toyoda
- 1950s – 1960s: Development of TPS by Taiichi Ohno
- 1960s – 1970s: TPS dissemination to the supply base
- 1984: Dissemination of TPS outside of Japan with the creation of the Toyota-General Motors joint venture – NUMMI – in California
- 1990: Widespread recognition of TPS as a model projection system grew with the publication of "The Machine That Changed the World"

Just-In-Time

- "Only what is needed, when it is needed, and in the amount needed"
- Elimination of waste, inconsistencies, and unreasonable requirements results in improved productivity

Kanban System

- The “Supermarket System”
- Using product control cards for product-related information to communicate which parts have been used
- Applied in JIT, by having the next customer in the process for to the preceding process to retrieve necessary parts they needed, when they needed them, in the amount the needed them.

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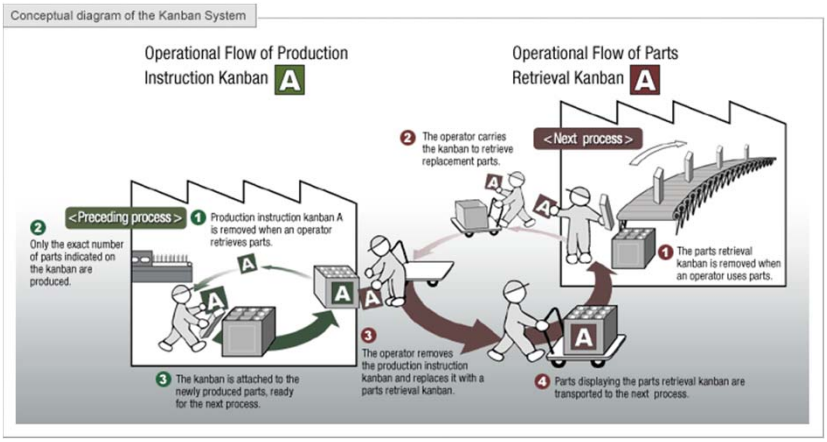
Kanban System



http://www.toyota-global.com/company/vision_philosophy/toyota_production_system/just-in-time.html

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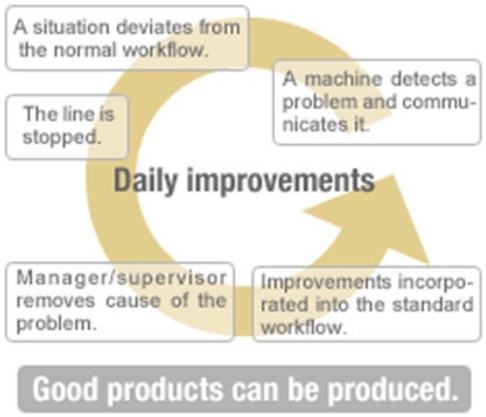
Jidoka

- "Automation with a human touch"
- Equipment stops when a problem arises
- A single operator can visually monitory and control many machines efficiently
- A single operator can be in charge of multiple machines thus improving productivity

Jidoka

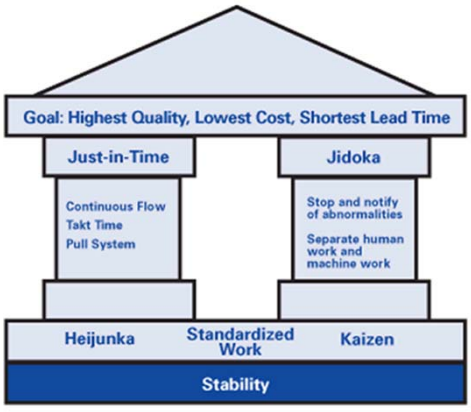


http://www.toyota-global.com/company/vision_philosophy/toyota_production_system/jidoka.html

Andon

- Jidoka and Visual Control
- Problem visualization
- An Andon is a display board system that allows operators to identify problems in the production line at a glance

Toyota Production System - House



Toyota Production System "House."

http://www.lean.org/lexicon/toyota-production-system

Toyota Production System

- Just-in-Time production, Jidoka and TPS House are maintained and improved through standardized work, kaizen, and by following the PDCA cycle (plan-do-check-act)

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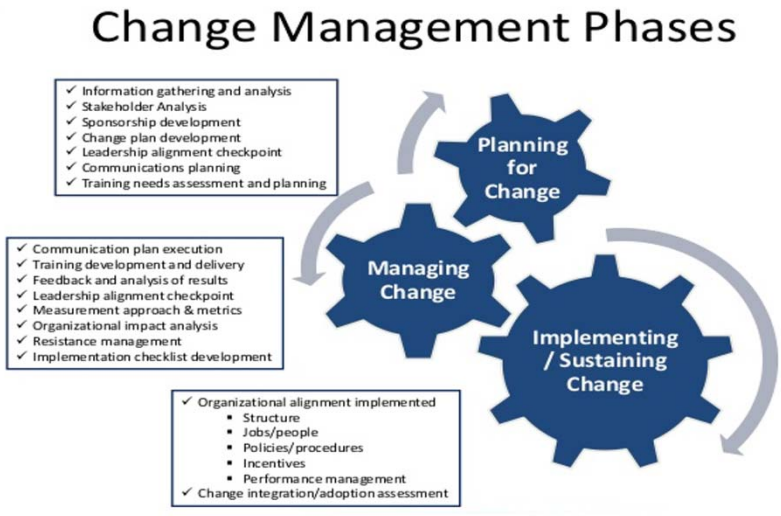
Thought of the week...



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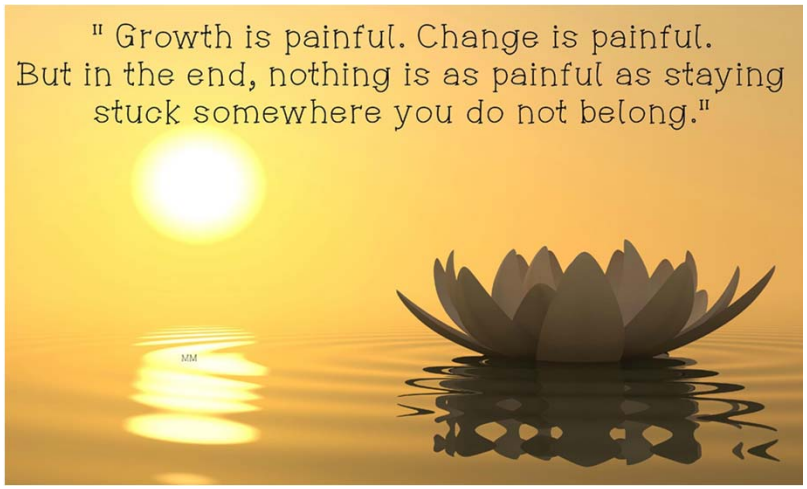

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Thank You

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Nick Vyas https://www.linkedin.com/in/thevyas007/ Email: nikhilvy@marshall.usc.edu Twitter: @TheNickVyas

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Wrap-Up!

Eunjoo Pacifici, PharmD, PhD

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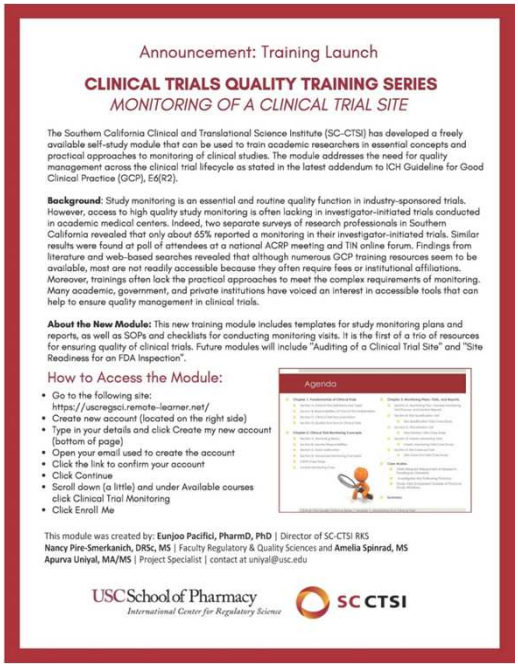
Monitoring Module & Clinical Research Professional Training



Announcement: Training Launch

CLINICAL TRIALS QUALITY TRAINING SERIES
MONITORING OF A CLINICAL TRIAL SITE

The Southern California Clinical and Translational Science Institute (SC-CTSI) has developed a freely available self-study module that can be used to train academic researchers in essential concepts and practical approaches to monitoring of clinical studies. The module addresses the need for quality management across the clinical trial lifecycle as stated in the latest addendum to ICH Guideline for Good Clinical Practice (GCP), E6(R2).

Background: Study monitoring is an essential and routine quality function in industry-sponsored trials. However, access to high quality study monitoring is often lacking in investigator-initiated trials conducted in academic medical centers. Indeed, two separate surveys of research professionals in Southern California revealed that only about 65% reported a monitoring in their investigator-initiated trials. Similar results were found at poll of attendees at a national ACRP meeting and TIN online forum. Findings from literature and web-based searches revealed that although numerous GCP training resources seem to be available, most are not readily accessible because they often require fees or institutional affiliations. Moreover, trainings often lack the practical approaches to meet the complex requirements of monitoring. Many academic, government, and private institutions have voiced an interest in accessible tools that can help to ensure quality management in clinical trials.

About the New Module: This new training module includes templates for study monitoring plans and reports, as well as SOPs and checklists for conducting monitoring visits. It is the first of a trio of resources for ensuring quality of clinical trials. Future modules will include "Auditing of a Clinical Trial Site" and "Site Readiness for an FDA Inspection".

How to Access the Module:

- Go to the following site: https://uscregsci.remote-learner.net/
- Create new account (located on the right side)
- Type in your details and click Create my new account (bottom of page)
- Open your email used to create the account
- Click the link to confirm your account
- Click Continue
- Scroll down (a little) and under Available courses click Clinical Trial Monitoring
- Click Enroll Me

Agenda

This module was created by: **Eunjoo Pacifici, PharmD, PhD** | Director of SC-CTSI RKS
Nancy Pire-Smerkanich, DRSc, MS | Faculty Regulatory & Quality Sciences and **Amelia Spinrad, MS**
Apurva Uniyal, MA/MS | Project Specialist | contact at uniyal@usc.edu

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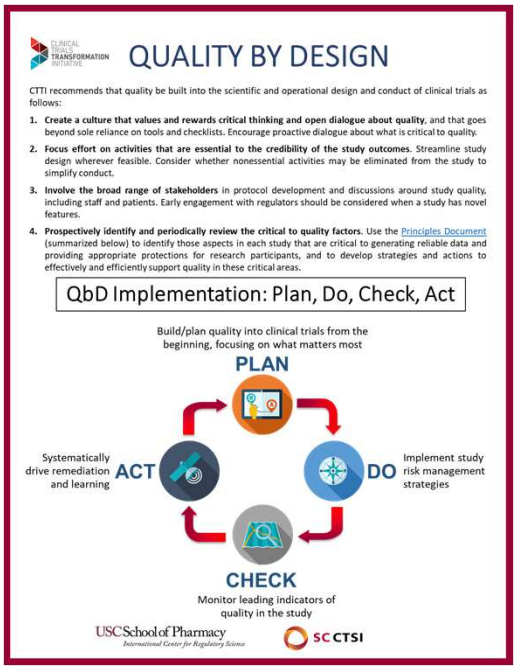
Quality by Design

CLINICAL TRIALS TRANSFORMATION INITIATIVE



CLINICAL TRIALS TRANSFORMATION INITIATIVE

QUALITY BY DESIGN

CTTI recommends that quality be built into the scientific and operational design and conduct of clinical trials as follows:

1. **Create a culture that values and rewards critical thinking and open dialogue about quality**, and that goes beyond sole reliance on tools and checklists. Encourage proactive dialogue about what is critical to quality.
2. **Focus effort on activities that are essential to the credibility of the study outcomes**. Streamline study design wherever feasible. Consider whether nonessential activities may be eliminated from the study to simplify conduct.
3. **Involve the broad range of stakeholders** in protocol development and discussions around study quality, including staff and patients. Early engagement with regulators should be considered when a study has novel features.
4. **Prospectively identify and periodically review the critical to quality factors**. Use the Principles Document (summarized below) to identify those aspects in each study that are critical to generating reliable data and providing appropriate protections for research participants, and to develop strategies and actions to effectively and efficiently support quality in these critical areas.

QbD Implementation: Plan, Do, Check, Act

Build/plan quality into clinical trials from the beginning, focusing on what matters most

PLAN

Systematically drive remediation and learning — ACT

DO — Implement study risk management strategies

CHECK

Monitor leading indicators of quality in the study

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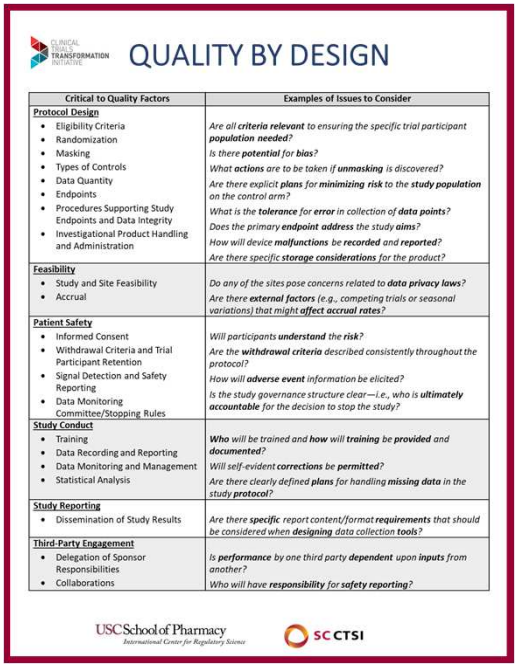
Quality by Design

CLINICAL TRIALS TRANSFORMATION INITIATIVE



CLINICAL TRIALS TRANSFORMATION INITIATIVE

QUALITY BY DESIGN

Critical to Quality Factors	Examples of Issues to Consider
Protocol Design • Eligibility Criteria • Randomization • Masking • Types of Controls • Data Quantity • Endpoints • Procedures Supporting Study Endpoints and Data Integrity • Investigational Product Handling and Administration	*Are all **criteria relevant** to ensuring the specific trial participant **population needed**?* *Is there **potential** for **bias**?* *What **actions** are to be taken if **unmasking** is discovered?* *Are there explicit **plans** for **minimizing risk** to the **study population** on the control arm?* *What is the **tolerance** for **error** in collection of **data points**?* *Does the primary **endpoint address** the study **aims**?* *How will device **malfunctions** be **recorded** and **reported**?* *Are there specific **storage considerations** for the product?*
Feasibility • Study and Site Feasibility • Accrual	*Do any of the sites pose concerns related to **data privacy laws**?* *Are there **external factors** (e.g., competing trials or seasonal variations) that might **affect accrual rates**?*
Patient Safety • Informed Consent • Withdrawal Criteria and Trial Participant Retention • Signal Detection and Safety Reporting • Data Monitoring Committee/Stopping Rules	*Will participants **understand** the **risk**?* *Are the **withdrawal criteria** described consistently throughout the protocol?* *How will **adverse event** information be elicited?* *Is the study governance structure clear—i.e., who is **ultimately accountable** for the decision to stop the study?*
Study Conduct • Training • Data Recording and Reporting • Data Monitoring and Management • Statistical Analysis	***Who** will be trained and **how** will **training** be **provided** and **documented**?* *Will self-evident **corrections** be **permitted**?* *Are there clearly defined **plans** for handling **missing data** in the study **protocol**?*
Study Reporting • Dissemination of Study Results	*Are there **specific** report content/format **requirements** that should be considered when **designing** data collection **tools**?*
Third-Party Engagement • Delegation of Sponsor Responsibilities • Collaborations	*Is **performance** by one third party **dependent** upon **inputs** from another?* *Who will have **responsibility** for **safety reporting**?*

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"Quality" in clinical trials is defined as:

Ensuring the trial is conducted according to protocol, GCP, SOP, and regulatory requirements

The absence of errors that matter to decision making

Ensuring all data collected for a study has been verified for accuracy

The absence of data corrections without proper initials and dating

What sector first originated the idea of quality by design?

Research

Farming

Manufacturing

Healthcare

Why is Quality by Design important?

It expedites site initiation and subject accrual

It expedites patient retention and study completion

It retrospectively reviews clinical trial data to determine if the study findings are robust

It prospectively examines the objectives of a trial and define factors critical to meeting these objectives

Three key principles of quality science include quality of end product, culture of productivity, and focus on consumer feedback.

True

False

Which of the following is NOT a QbD recommendation from CTTI?

- Focus efforts on activities essential to credibility of outcomes
- Focus on creating useful tools and checklist
- Involve broad range of stakeholders in protocol development
- Prospectively identify and periodic review quality factors

What is an example of a factor critical to quality?

- Path to reimbursement for innovative products
- Design of the study protocol
- Time to study initiation
- Completion of study enrollment

Understanding what is critical to quality results in a focused monitoring and auditing plan.

True

False

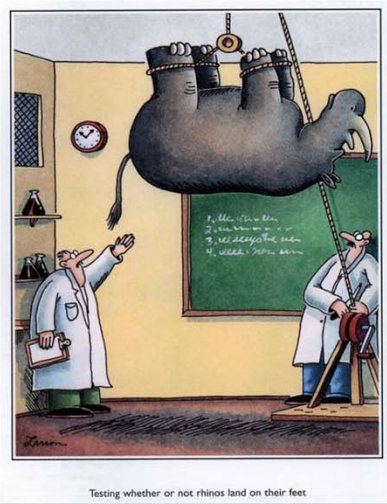
Start the presentation to see live content. Still no live content? Install the app or get help at PollEv.com/app

What is not a barrier to QbD implementation?

Difficulty overcoming organizational inertia	A
Fear of change	B
Concern it would take more time and create more work	C
Lack of understanding in QbD value	D
All of the above are barriers	E

Start the presentation to see live content. Still no live content? Install the app or get help at PollEv.com/app

Has QbD been applied to this experiment?



Testing whether or not rhinos land on their feet

What's QbD?

Definitely!

Maybe …

No way!

Start the presentation to see live content. Still no live content? Install the app or get help at PollEv.com/app

Presented by the USC School of Pharmacy International Center for Regulatory Science and the Southern California Clinical and Translational Science Institute

This certifies that

The program evaluation has been sent to your email address.

Please email the completed program evaluation to Apurva Uniyal (uniyal@usc.edu) to receive a certificate of completion by Friday, March 20, 2020.

Eunjoo Pacifici, PharmD, PhD
Director
International Center for Regulatory Science

Thomas A. Buchanan, MD
Director
Southern California Clinical and Translational Science Institute

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USC Regulatory Science | regulatory.usc.edu

Phone: (323) 442-3521

Email: regsci@usc.edu

Facebook: @RegSci

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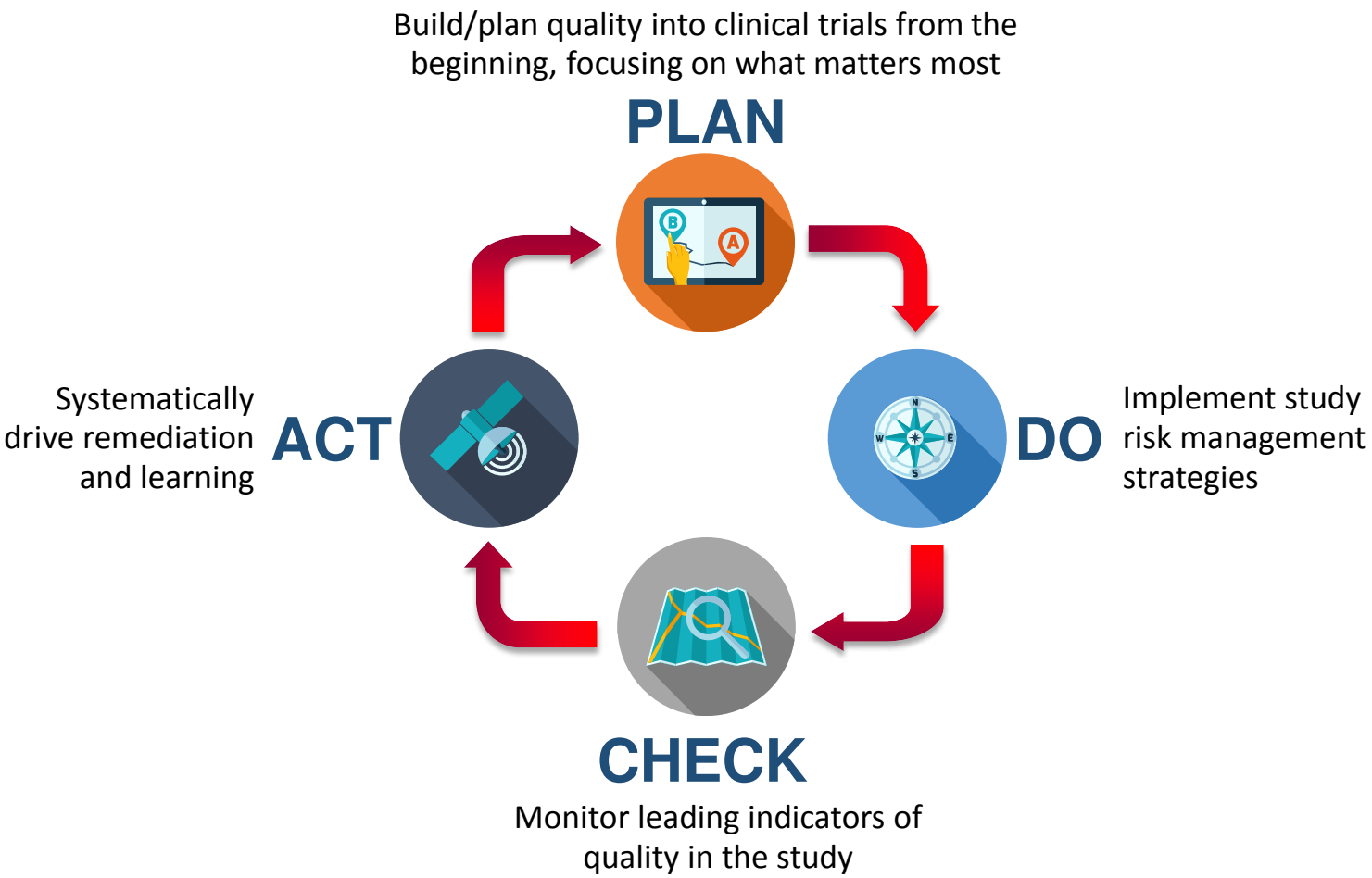

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Regulatory Science Symposium Survey

Please email the completed survey to Apurva Uniyal (uniyal@usc.edu) to receive a certificate

1) Have you attended a previous symposium?
   a) Yes
   b) No, this is my first symposium.

   1A. If yes, did you find the content of the program relevant to your daily work activities?
   a) Yes
   b) No

   1B. How useful was the content for your daily work activities?
   a) Extremely useful
   b) Somewhat useful
   c) Not useful

2) How would you rate the level of content of today's program?
   a) Too hard
   b) Too easy
   c) Just right

3) How would you rate the delivery of content of today's program?
   a) Very good
   b) Good
   c) Average
   d) Poor
   e) Very poor

4) Did you make new connections with other research professionals through the networking activity?
   a) Yes
   b) No, please explain: _____

   _____

   _____

5) How would you rate the length of today's program?
   a) Too long
   b) Too short
   c) Just right

6) How would you rate the quality of today's venue?
   a) Very good
   b) Good
   c) Average
   d) Poor
   e) Very poor

7) How would you rate the organization of today's event?
   a) Very good
   b) Good
   c) Average
   d) Poor
   e) Very poor

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8) Would you attend these offerings in the future?
   a) Yes
   b) No

9) Overall, how would you rate today's program?
   a) Very good
   b) Good
   c) Average
   d) Poor
   e) Very poor

10) Are there any unusual/challenging ethical issues you have encountered or would like to learn about?

_____
_____
_____
_____

11) Do you have any suggestions for topics for a future program(s).

_____
_____
_____
_____