Transforming the Quality of Clinical Trials and Reestablishing Trust in Translational Research

Quality-by-design and Critical-to-Quality Design Studios

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from lab to life.

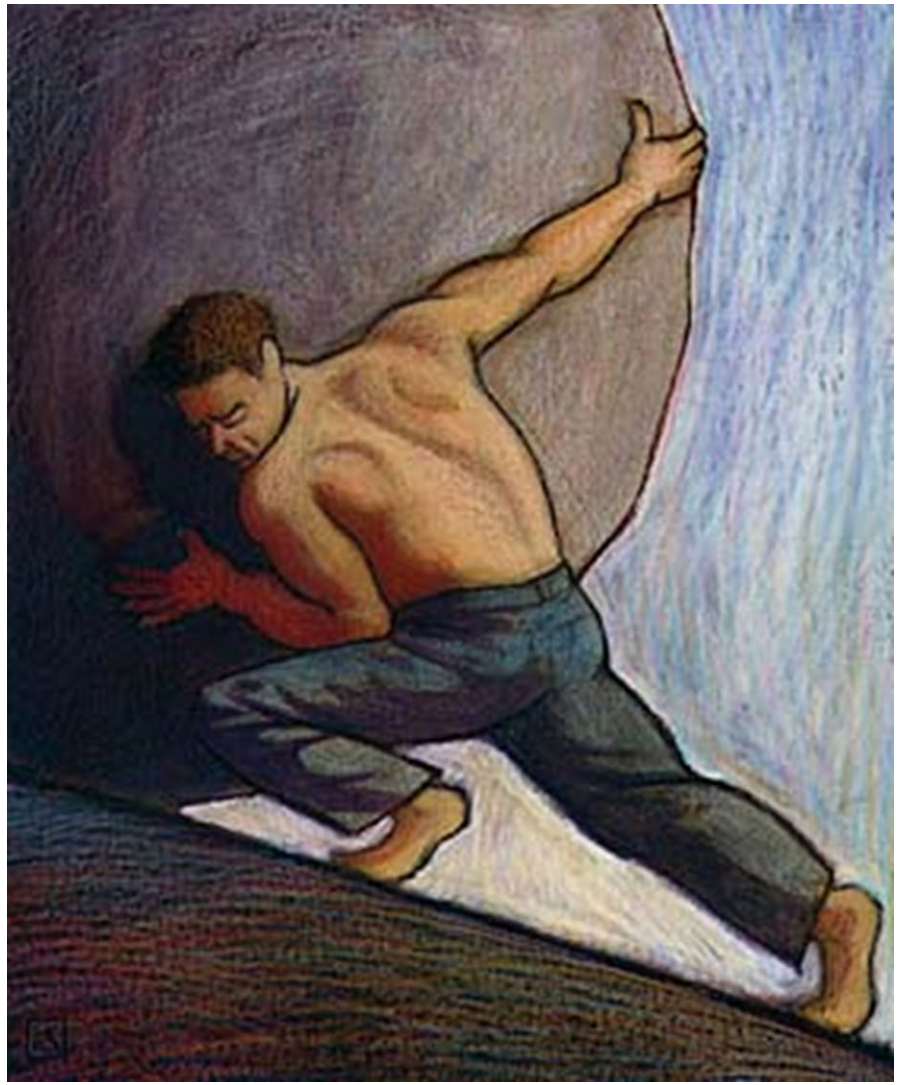
Topics for today (the Science of Translation and All That Jazz)

1. The challenge—Mistrust of the clinical trial enterprise
2. The concept of Quality-by-Design (and how it revolutionized the automobile industry)
3. What are Critical-Quality-Factors (CTQs) in clinical research
4. Developing QbD Studios at academic health centers
5. Some use-cases
6. Next steps

“Quality” in clinical and translational science

The lack of errors that matter, mainly those which compromise the integrity and reliability of clinical trial data or the safety of participants and patients.

1. The challenge—Mistrust of the clinical trial enterprise



Anaesthesia 2021, 76, 472–479 doi:10.1111/anae.15263

Original Article

False individual patient data and zombie randomised controlled trials submitted to *Anaesthesia*

J. B. Carlisle[1,2]

The review of individual patient data of submitted randomised controlled trials revealed ***false data in 44%.*** *I think journals should assume that all submitted papers are potentially flawed and editors should review individual patient data before publishing randomised controlled trials*

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HOW MANY CLINICAL TRIALS CAN'T BE TRUSTED?

Investigations suggest that, in some fields, at least one-quarter of clinical trials might be problematic or fake, warn researchers. They urge stronger scrutiny. **By Richard Van Noorden**

Nature | Vol 619 | 20 July 2023 |

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Some Causes of Poor Quality in Clinical Research

Costs of poor-quality clinical trials

- **$$$$** e.g., the expenses for **initiating sites that do not perform**--a site costs from $20,000 to $30,000, and maintaining a site is estimated to be $1,500 per month.
- **Trust** in the clinical research enterprise—e.g., enormous health problems likely to occur as vaccination compliance decreases
- Exacerbate **health disparities and inequities**
- Profound **individual suffering**

The New York Times

F.D.A. Revokes Approval of Avastin for Use as Breast Cancer Drug

Share full article 139

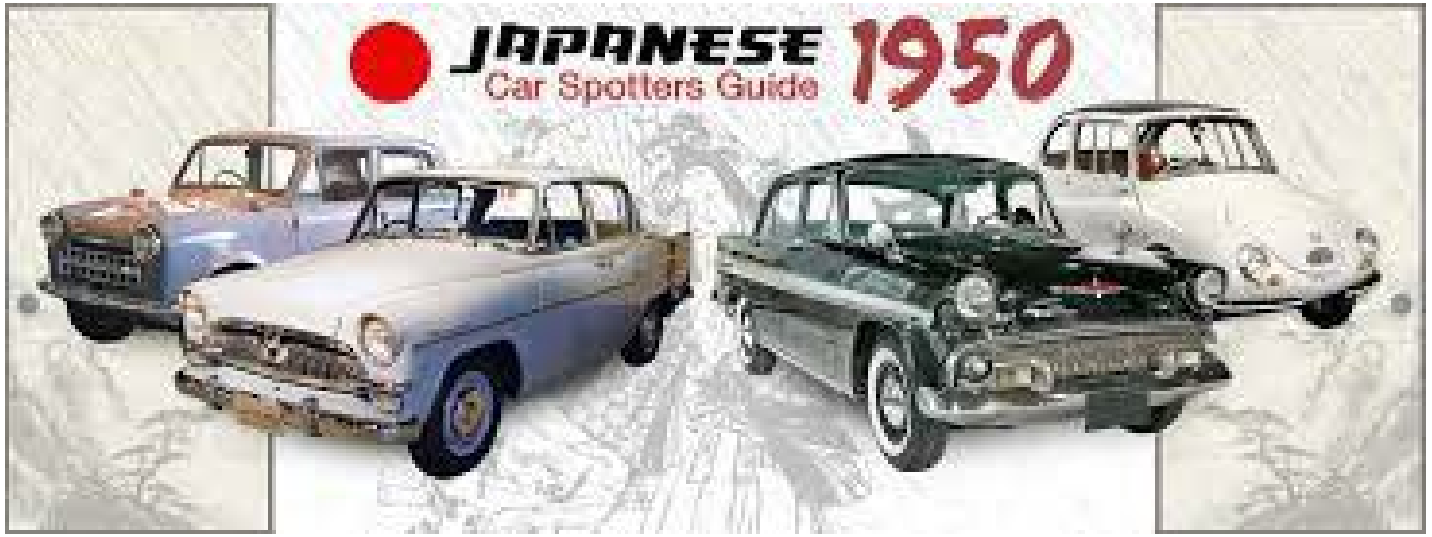
By Andrew Pollack

Nov. 18, 2011

The commissioner of the Food and Drug Administration on Friday revoked the approval of the drug Avastin as a treatment for breast cancer, ruling on an emotional issue that pitted the hopes of some desperate patients against the statistics of clinical trials.

"I'm disappointed the commissioner has chosen to take the hardest line possible," Terrence D. Kalley of Troy, Mich., whose wife, Arlene, has been taking Avastin, said Friday. Mr. Kalley, who organized a protest outside the F.D.A. hearing in June, said that for some women, Friday's decision was "nothing short of a death sentence."

2. The concept of Quality-by-Design (and how it revolutionized the automobile industry)



mid-1950's. Things were so bad in the Japanese automobile industry that the Japanese Prime Minister refused to be driven in domestic-made cars for fear they would break down.

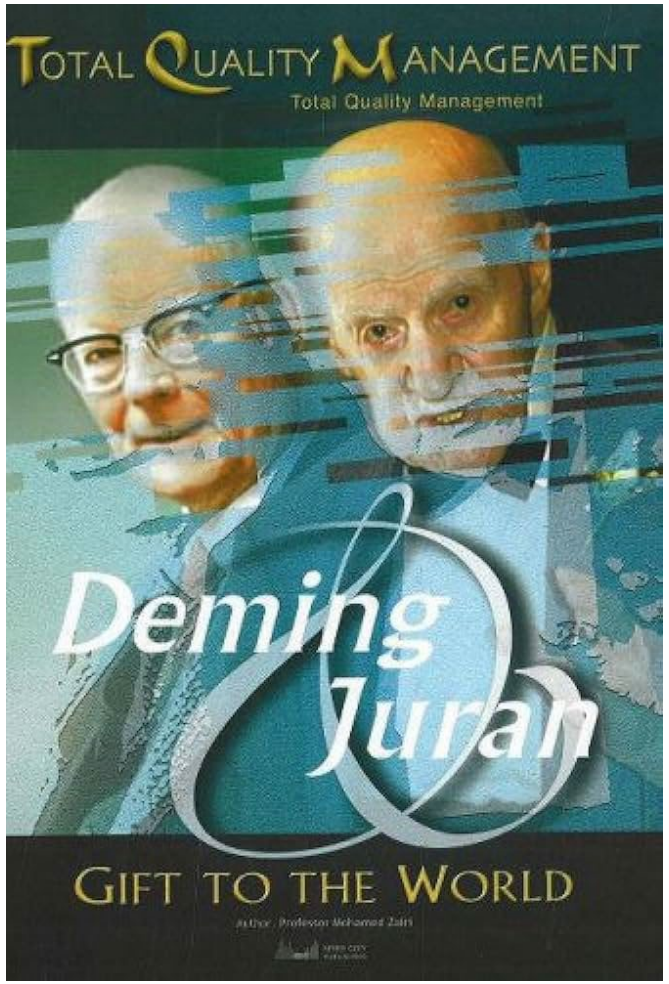
Ichirō Hatoyama

In 1980 Japan becomes the largest auto-producing country in the world, with a reputation for reliable cars and detail-oriented engineering.

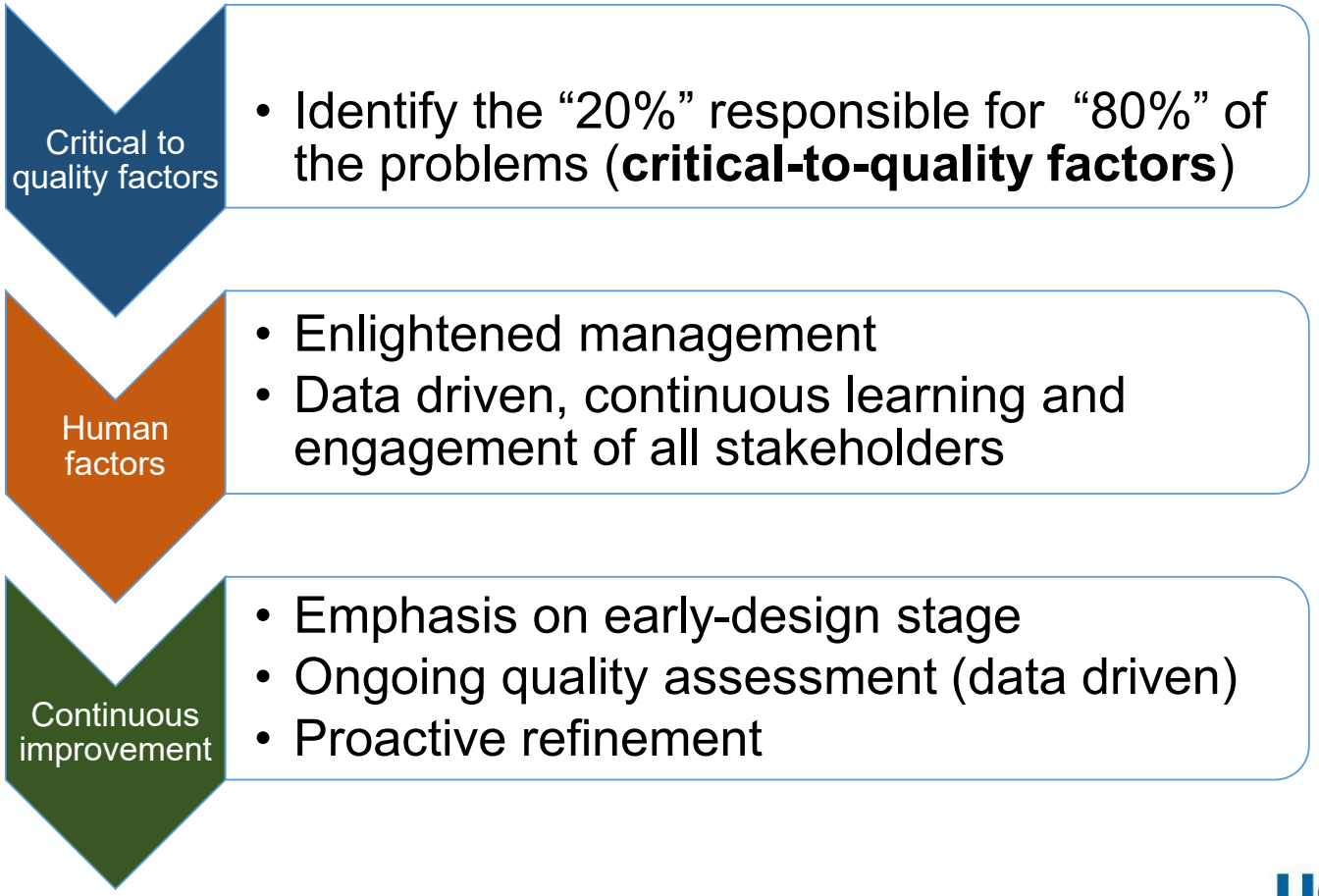
- Workers on each side move briskly to unbolt the mazda doors
- Doors are removed and placed on separate conveyors.
- Not be reattached until the car is almost complete.
- **That is not the way it is done in most car factories, where manufacturers are usually satisfied to hang the doors, check them for reasonable fit and proceed with the assembly.**

Pioneers of Quality in Manufacturing: Juran and Deming (1950s)

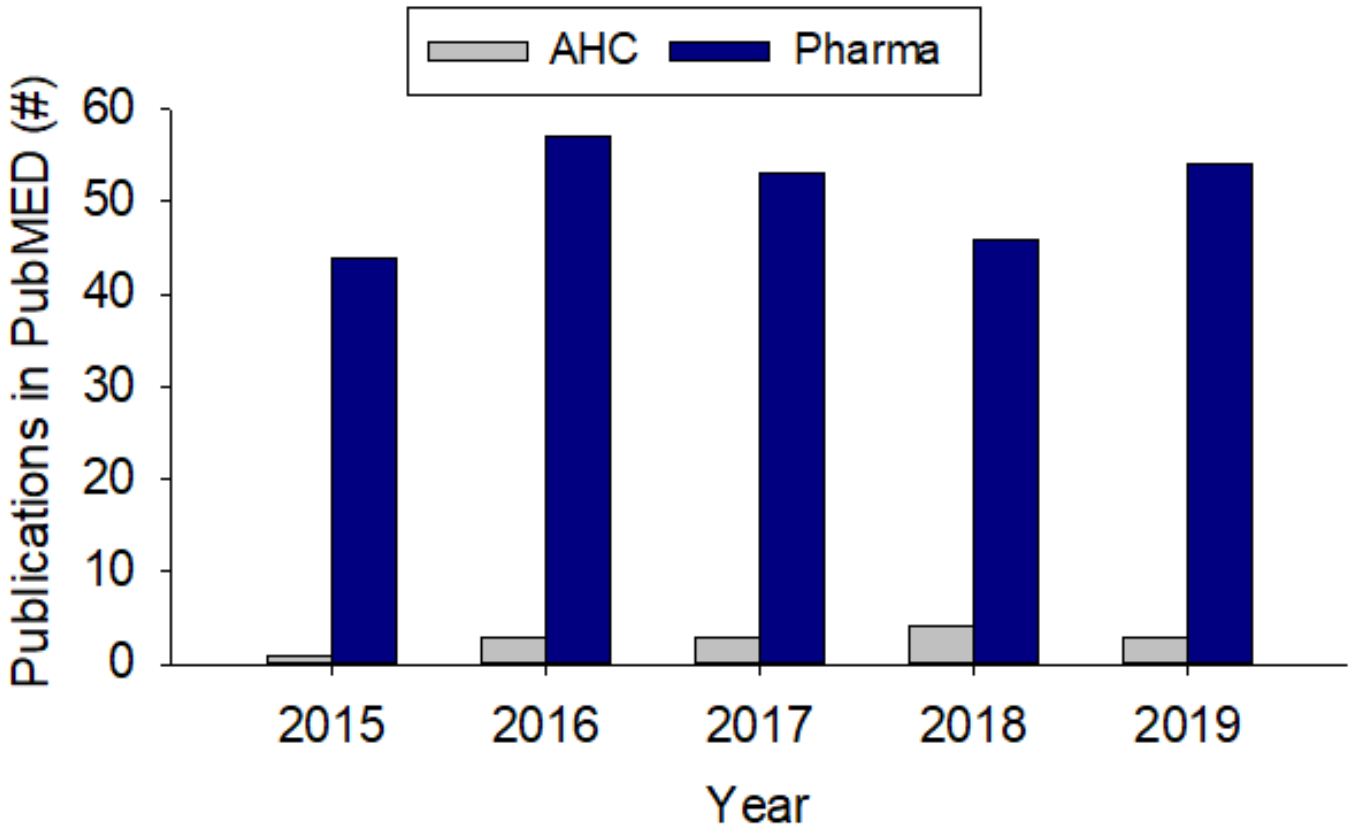
- Created **systematic approaches to quality improvement**.
- Upended the common practice of judging quality solely by examination of the end product, to one which focused on key elements across the whole manufacturing process **from start to finish**.
- Insisted on **data-driven and statistically sound evaluation** of all process components.
- Expanded the scope of quality improvement beyond sole inspection of a process component to include a **wider examination of the human dimension** by focusing on the need for:
  - ✓ enlightened management
  - ✓ constant learning
  - ✓ mitigating resistance to change



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



Failure of AHCs to Implement QbD



The QbD gap in academic health centers. A pubmed search of "**quality-by-design**" and either "**pharma**" or "**academic health center/school of medicine**" revealed large differences in publications between pharma/industry and AHCs.

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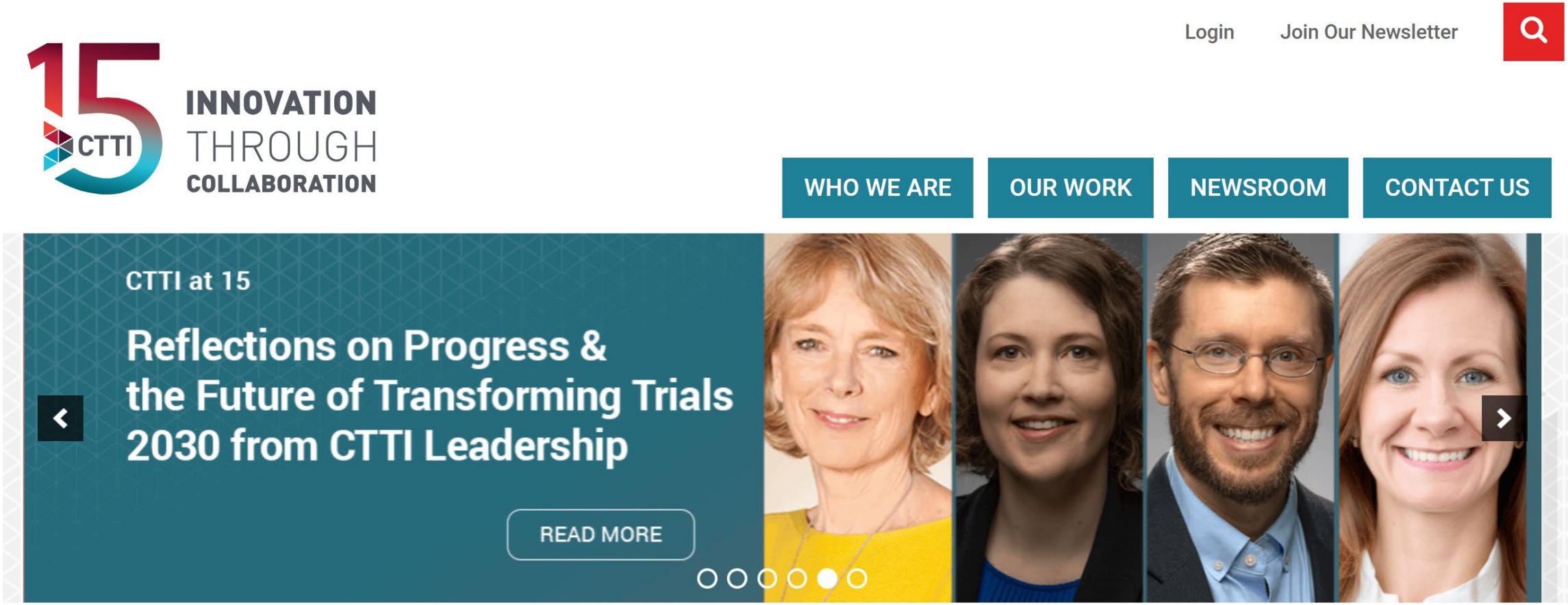
Failure of AHCs to Implement QbD

- the more hierarchical structure of industry facilitates top-down implementation of new processes
- the skepticism of AHC faculty to embrace possibly meretricious and formulaic approaches to complex problems
- a sense among AHC faculty that they “already know” and do not require formal training to embed quality in clinical trials.

Clinical Trials Transformation Initiative (CTTI) https://ctti-clinicaltrials.org/



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QbD in Clinical Research

QUALITY BY DESIGN

HOME - OUR WORK - QUALITY - Quality By Design

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SOCRA
FOR CLINICAL RESEARCH EXCELLENCE

CONFERENCES & EDUCATION | CERTIFICATION | MEMBERSHIP | ANNUAL CONFERENCE

CERTIFICATION

Quality by Design for Clinical Trials

Program Overview
Certification Program
CCRP Certification Exam
Exam Schedule SOCRA Sponsored Sites
Maintenance of Certification
Recertification
Accreditation

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from lab to life

3. What are Critical-Quality-Factors (CTQs) in clinical research

Critical to Quality Factors in Clinical Research

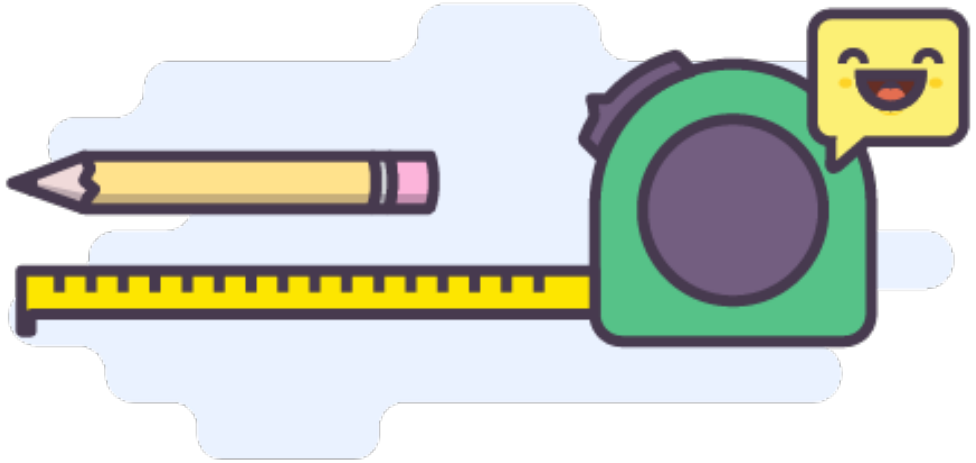
- ✓ CTQ factors are the attributes or features of a product or service that directly affect customer satisfaction and expectations.
- ✓ They are derived from the voice of the customer, which is the feedback and input from the end users or beneficiaries of your processes.

Critical to Quality Factors in Clinical Research

Measurable

Can be prioritized

Amenable to evaluation



Critical to Quality Factors in Clinical Research

Cateogories and selected examples of CtQ factors* in clinical trials (developed by ctti and the project team)

PROTOCOL DESIGN

Eligibility Criteria	Are all criteria relevant to ensuring the specific trial participant population needed for the trial?
Social Determinants	Does the study design address recruitment and operationalization factors such as race, socioeconomic status, gender, or geographical considerations.
Procedures	Do “errors that matter” cluster in any specific area or procedure?

FEASIBILITY

Site	Does the research team have institutional support to engage in the research?
Retention	Do trial participants have personal issues that can be mitigated to aid retention in the research (i.e., transport, babysitting, stigma, translation services)?
Data monitoring	Is the study governance structure clear—i.e., who is ultimately accountable for the decision to stop the study?

Critical to Quality Factors in Clinical Research

PATIENT SAFETY	
Informed consent	What are the key elements of the informed consent process for this study?
Signal Detection	Are standard definitions for adverse events provided in the protocol?

STUDY CONDUCT	
Training	Do trial participants need specific training?
Statistical analysis	Are there measures to ensure that study statisticians are aware of the clinical implications of study objectives and endpoints?

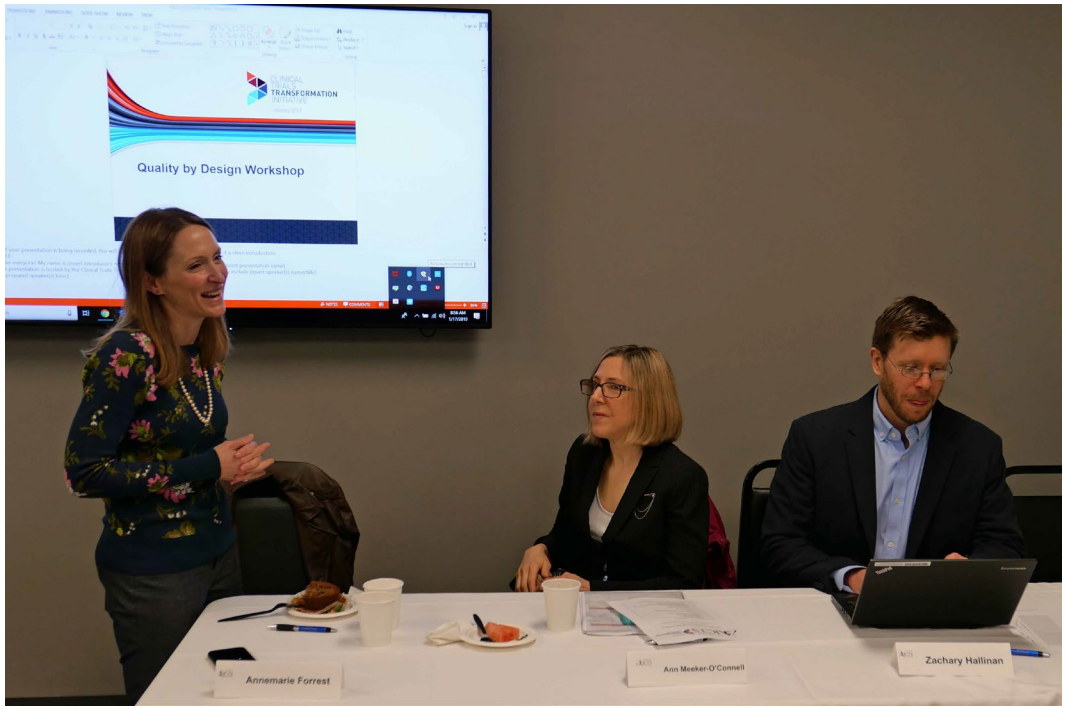
STUDY REPORTING	
Dissemination	Is it clear who has the right to prepare publications and reports using the study data?

***CTTI developed 149 examples of CTQs for the categories listed in the Table**

4. Developing QbD Studios at academic health centers

Our Approach: Adapting the **Design Studio** approach to QbD

- Clinical and translational research studios were elegantly described and articulated by Byrne and colleagues at Vanderbilt [Acad Med. 2012;87(8):1052-9].
- The format was developed as a “series of integrated, dynamic, and interactive roundtable discussions that bring relevant research experts from diverse academic disciplines together to focus on a specific research project at a specific stage.”
- The objective was to build a more robust engagement between medicine, systems engineering, management science, and information science to facilitate more rigorous, efficient, and modern methods of research.



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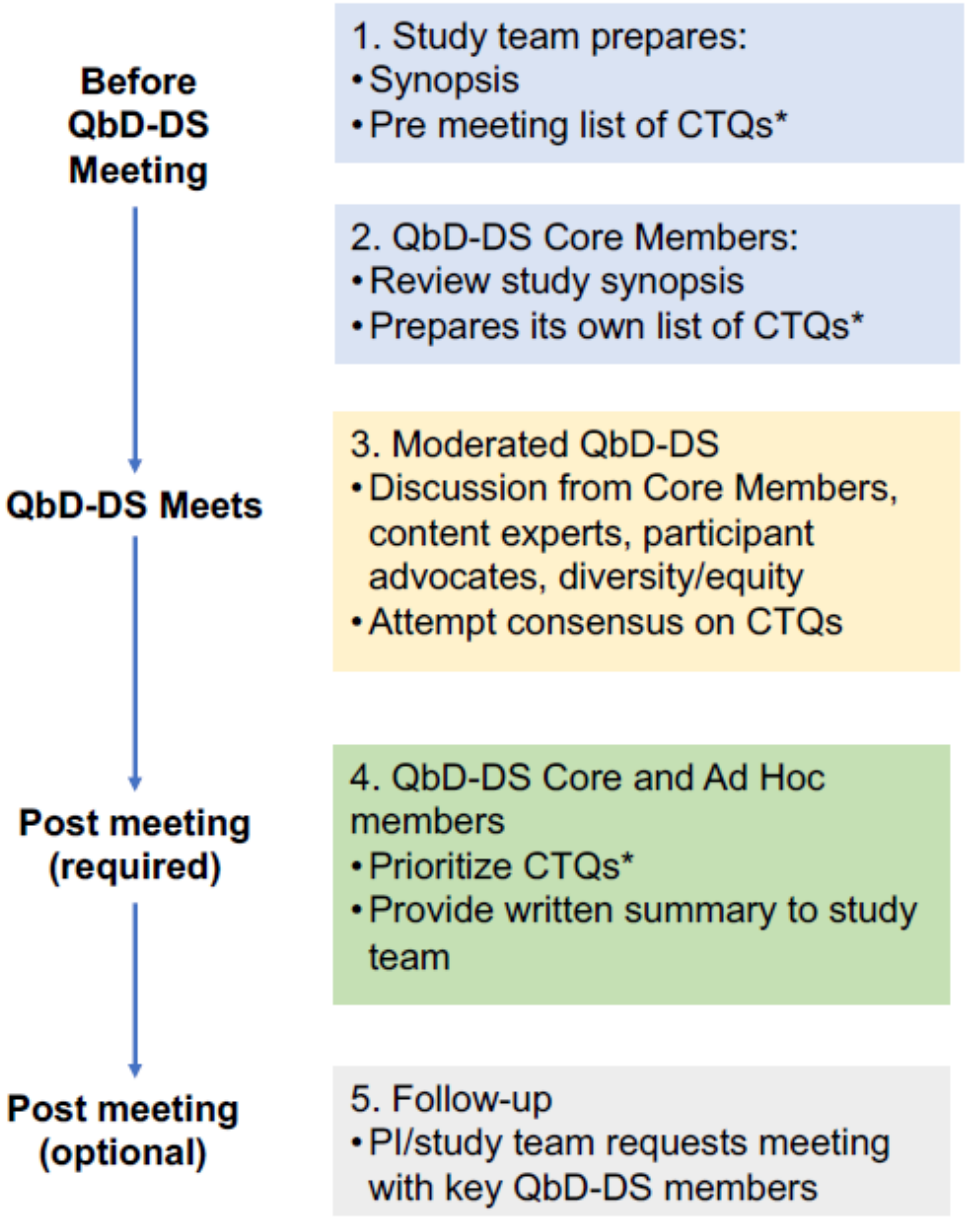
Structure of the QbD Design Studio

Core Member Expertise/Role
• Moderator
• PI and Clinical Coordinators of the study under review
• Content Expert(s)
• Participant Advocate
• Bioethics
• Biostatistics

• Clinical Trialist
• Equity and Diversity
• Recruitment and Retention
• Dissemination and Implementation
• Meeting Evaluator
• Ad Hoc Attendees
• Learners (K or T awardees; health science students)

Structure of the QbD Design Studio



*Critical to Quality categories per CTTI guidelines

5. Some use-cases

QbD Design Studios--Examples

Study Title	Participant Advocate	CTQ-Related Insight (per CTTI Category)
SGLT2 Inhibitors and the Gut Microbiome	Patient with type 1 diabetes	**Feasibility:** Recruit in the clinic on the day of the visit to minimize study participation duration.
Phase 1/2a Study of the Safety and Tolerability of neurosurgical stem cell transplantation for a rare neurologic disorder	Patient advocate who had lost several family members to the disorder	**Study conduct:** Construct a detailed plan for explaining the meaning of a placebo-controlled study for patients with the potential of developing the rare disorder.
The Nutrient Trial: Nutritional Intervention Among Myeloproliferative Neoplasms	Patient with myeloproliferative neoplasms	**Patient safety:** Need to monitor to ensure that patient is not experiencing a weight maintenance issue.

QbD Design Studios--Examples

Convalescent Plasma in patients with COVID-19 (randomized clinical trial)	Recovered COVID-19 patient who volunteered to donate	**Protocol design:** Effective messaging for participant recruitment should be developed with input from the target population.
The Effect of Mitigation Procedures to Inhibit COVID-19 Transmission as K-12 Schools Reopen	Mother and daughter of 6th grader in one of the selected schools	**Patient safety:** Make every attempt to not identify and possibly embarrass the students who volunteer for the study.
Dietary Sodium Intake and Blood pressure in Living Kidney Donors: Single-Blind Randomized Controlled Trial	Healthy subject post kidney donation	**Protocol design:** The eligibility window for recruitment should take into account the post-surgical recovery period, during which patients may be in pain and/or taking pain meds.

QbD Design Studios--Examples

ACTIV-1 IM: randomized master protocol for immune modulators for treating COVID-19	Patient who had recovered from COVID19 infection	**Feasibility:** This study has daily data collection and will take a lot of effort and coordination. Therefore, budget and staffing needs should be assessed and addressed in preparation of study conduct/monitoring.
Serosurveillance of UCI Health Staff for SARS-CoV-2 Antibodies during COVID-19 Outbreak using a Coronavirus Antigen Microarray	Health staff working at the medical center.	**Study conduct:** At least one member of the DSMB should be from outside UCI to minimize the potential for unconscious bias.

QbD Design Studios—Multicenter with UAMS

Magnetoencephalography (MEG) to identify neurodevelopmental disabilities in children with congenital heart disease	Parent of child with history of congenital heart disease	**Feasibility:** This study has procedural elements that require much effort and coordination. Skilled outreach to parents and participants is necessary.
Therapeutic efficacy of human preterm human umbilical cord derived mesenchymal stem cell conditioned medium for neonatal chronic lung disease	Parent of child born prematurely and hospitalized for 2 months in the NICU.	**Study conduct:** More detail is needed on inclusion criteria and balance of enrollment. The current design does not acknowledge that fetal lung maturity (different across gestational ages) may impact the efficacy of the intervention.

CTQ Scoring

Summary of Critical to Quality (CTQ) Factor Ranking

QbD Committee members were asked via a REDCap survey to rate each Critical-to-Quality (CTQ) factor as “high”, “medium” or “low” priority, using the following definitions:

High (3): This factor is indeed critical to the integrity of the research. If the investigators do not attend to this concern, the study is at high risk for failure, either in terms of an inability to execute the protocol (e.g.., recruit adequate participants) or in terms of a design flaw that will greatly reduce confidence in the findings.

Medium (2): This factor has the potential to threaten the feasibility of and/or confidence in the study. The quality of the data and/or the strength of the results are highly likely to be meaningfully improved by attending to this factor.

Low (1): This factor should be acknowledged as a potential threat to study integrity. If resources or pragmatic concerns prevent the investigators from addressing this concern, the study should still proceed, but the investigators should anticipate and plan for challenges related to this factor.

CTQ Scoring

CTQ Factor	Median Score
The study summary should clarify how safety reporting will occur and how signals will be detected.	2.9
If safety has already been established in a phase I or phase IIa study, then efficacy can be primary endpoint. However, safety should still be one of the endpoints for the study.	2.9
Include signal detection and safety reporting elements.	2.8
The study is attempting to address an important problem of BPD in premature infants but needs to demonstrate safety in vulnerable population.	2.7
The study summary should address what safety signals the Independent Data Monitoring Committee will review and what criteria it will use to determine whether further interventions are warranted following the pre-specified interim analysis. In particular, the summary should address what stopping rules will be in effect.	2.7
Stratifying randomization by gestational age and severity of condition at delivery can be helpful in avoiding imbalance between the two groups.	2.6
More detail is needed on inclusion criteria and balance of enrollment. The current design does not acknowledge that fetal lung maturity (different across gestational ages) may impact the efficacy of the intervention.	2.6
Conduct a power analysis in regard to number of subjects needed.	2.5

6. Next steps

QbD and the Science of Translation

Figure C1-2. "Talking Translation–A Dialogue with Physicians and Scientists." This 11-min video is effective in initiating learning opportunities in principles and practice of CTS&R.

CTSA Program Focus

Develop, demonstrate, and disseminate innovations that turn science into medicine faster

Provide a national resource for the rapid response to urgent public health needs

Promote impactful partnerships and collaborations

Promote training and career support

Address health disparities

Nurture field of translational science

Questions?

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