Building Quality into the Design and Conduct of Clinical Studies: Integrating Quality by Design (QbD) and Risk-Based Monitoring (RBM) Approaches

January 31, 2024
9:00 a.m. – 4:20 p.m. ET

FDA U.S. FOOD & DRUG ADMINISTRATION

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Welcome

Mark McClellan

Director, Duke-Margolis Institute for Health Policy

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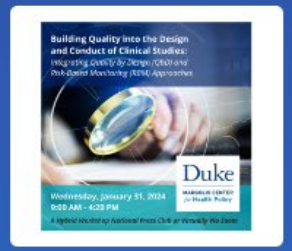
Workshop Agenda

9:00 AM	**Welcome**
9:10 AM	**Opening Remarks**
9:20 AM	**Risk-Based Approaches to Building Quality into the Design and Conduct of Clinical Investigations - Regulatory Perspectives of QbD and RBM**
10:35 AM	**Break**
10:45 AM	**Optimizing Study Design and Setting the Stage for Efficient Study Conduct Through QbD: Successes and Challenges**
12:15 PM	**Break for Lunch**
1:25 PM	**Translating QbD Principles to Risk-Proportionate Oversight Including RBM: Successes and Challenges**
2:55 PM	**Break**
3:10 PM	**Next Steps for Implementing Quality Management of Clinical Investigations**
4:10 PM	**Concluding Remarks**
4:20 PM	**Adjournment**



Join at

slido.com

#QBD

Opening Remarks

Janet Woodcock

Principal Deputy Commissioner, U.S. Food and Drug Administration

Session 1: Risk-Based Approaches to Building Quality into the Design and Conduct of Clinical Investigations - Regulatory Perspectives of QbD and RBM

Moderator: **Jacqueline Corrigan-Curay,** US Food and Drug Administration

Speakers:

M. Khair ElZarrad, US Food and Drug Administration

Fergus Sweeney, Clinical Trials Expert, Retired

David Nickerson, PhRMA

Kerstin Koenig, EFPIA

U.S. FOOD & DRUG ADMINISTRATION
OFFICE OF MEDICAL POLICY

Modernizing Clinical Trial Design & Conduct

M. Khair ElZarrad, PhD, MPH

Director, Office of Medical Policy
Center for Drug Evaluation and Research
US Food and Drug Administration

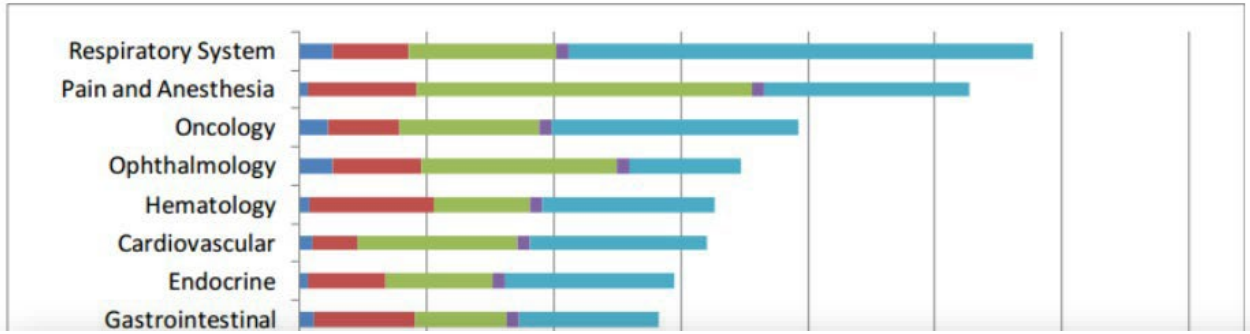
Jan 2024

Summary

- Modernizing the Clinical Trial Enterprise
- Recent Guidances
  - Risk-Based Monitoring Guidances
  - ICH E6(R3) Good Clinical Practice Guideline (*draft)*
- Conclusion

We (still) need to do better….

Figure 3: Clinical Trial Costs (in $ Millions) by Phase and Therapeutic Area



Contents lists available at ScienceDirect

Contemporary Clinical Trials Communications

journal homepage: www.elsevier.com/locate/conctc

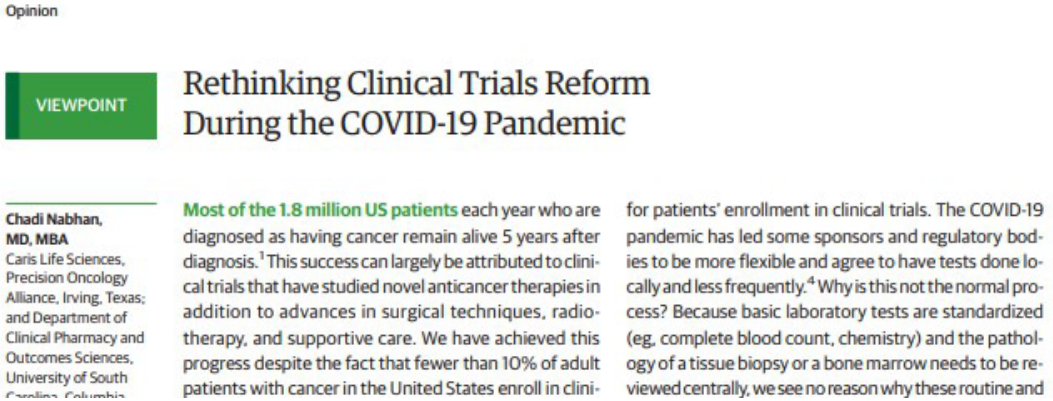
ELSEVIER

Factors associated with clinical trials that fail and opportunities for improving the likelihood of success: A review

David B. Fogel

Trials.ai, 4520 Executive Dr., Suite 200, San Diego, CA, 92121, United States

Many trials are costly, protracted, complex, and lagging in incorporating innovations…..



Opinion

VIEWPOINT

Rethinking Clinical Trials Reform During the COVID-19 Pandemic

Chadi Nabhan, MD, MBA
Caris Life Sciences, Precision Oncology Alliance, Irving, Texas; and Department of Clinical Pharmacy and Outcomes Sciences, University of South Carolina, Columbia

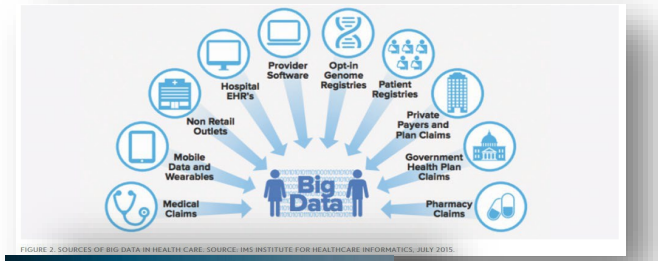
Most of the 1.8 million US patients each year who are diagnosed as having cancer remain alive 5 years after diagnosis.[1] This success can largely be attributed to clinical trials that have studied novel anticancer therapies in addition to advances in surgical techniques, radiotherapy, and supportive care. We have achieved this progress despite the fact that fewer than 10% of adult patients with cancer in the United States enroll in clinical trials for patients' enrollment in clinical trials. The COVID-19 pandemic has led some sponsors and regulatory bodies to be more flexible and agree to have tests done locally and less frequently.[4] Why is this not the normal process? Because basic laboratory tests are standardized (eg, complete blood count, chemistry) and the pathology of a tissue biopsy or a bone marrow needs to be reviewed centrally, we see no reason why these routine and

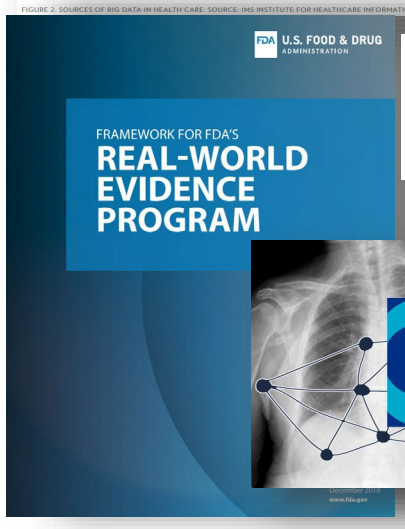
- During the COVID-19 pandemic, many trials did not produce generalizable result (e.g., too small and sometimes single-arm)
- However, there are examples of trials taking advantage of healthcare infrastructure, incorporating robust study design, utilizing technology, and producing reliable results

https://aspe.hhs.gov/reports/examination-clinical-trial-costs-barriers-drug-development-0 https://guides.clarahealth.com/clinical-trial-safety/ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6092479/pdf/main.pdf https://jamanetwork.com/journals/jamaoncology/fullarticle/2769129 https://www.nihr.ac.uk/blog/improving-clinical-trials-keep-the-focus-on-the-participants/25454

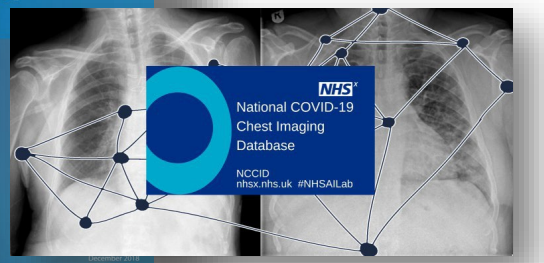
Facilitating Rapidly Evolving Ecosystem

Advancing Evidence Generation Paradigm*

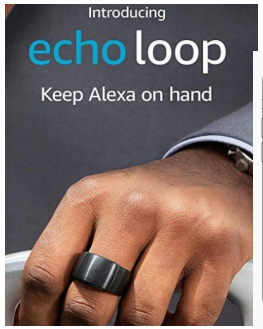


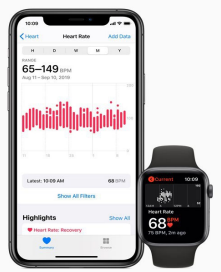


HDRUK
Health Data Research UK



Increasingly Digital World & Data Availability





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Ada Health Medical

Everyone

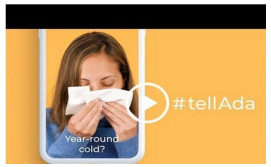
Add to Wishlist

INNOVATION

Using AI to Improve Electronic Health Records

by Thomas H. Davenport, Tonya M. Hongsermeier, and Kimberly Alba Mc Cord

December 13, 2018



KHN

COVID-19 | VACCINES | RACE & HEALTH | INVESTIGATIONS | MORE TOPICS | PODCASTS | DONATE

Your Wake-Up Call On Data-Collecting Smart Beds And Sleep Apps

Innovative Clinical Trial Designs*

Complex Innovative Trial Designs Pilot Program

Share | Tweet | LinkedIn | Email | Print

CLINICAL TRIALS TRANSFORMATION INITIATIVE

PROJECT:

Decentralized Clinical Trials

CADTH Evidence Driven.

Summary

Adaptive and Novel Trial Designs

*Samples

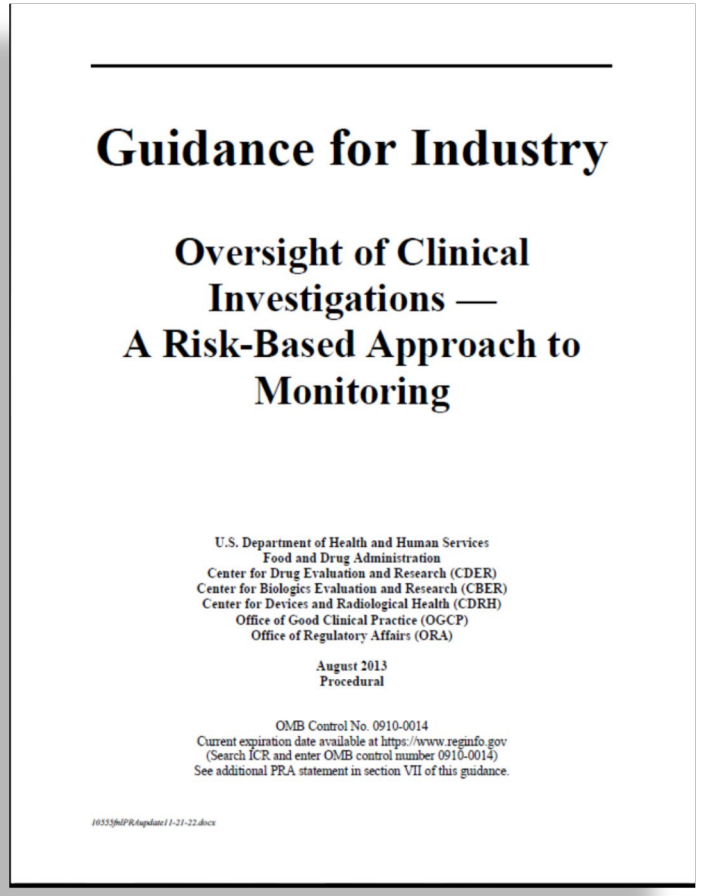
Modernizing Clinical Trials

- Promoting *efficiency, flexibility, and innovation* while ensuring participant protections and the reliability of trial results
- Implementation of *proportionate and risk-based* quality management starting at the study design phase and continuing throughout the conduct and analysis of a trial
- Cornerstones of a risk-based quality management approach include:
  - Fitness for purpose
  - Quality by design
  - Risk-based quality management

FDA Efforts to Support QbD and RBM

- Outreach and collaboration with academia, industry, international partners, and other interested parties
- Guidance documents:
  - Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring (2013)
  - A Risk-Based Approach to Monitoring of Clinical Investigations Questions and Answers (2023)
  - ICH E8(R1) General Considerations for Clinical Studies (2022)
  - ICH E6(R3) Good Clinical Practice (*draft*, 2023)

Risk-Based Monitoring



Guidance for Industry

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

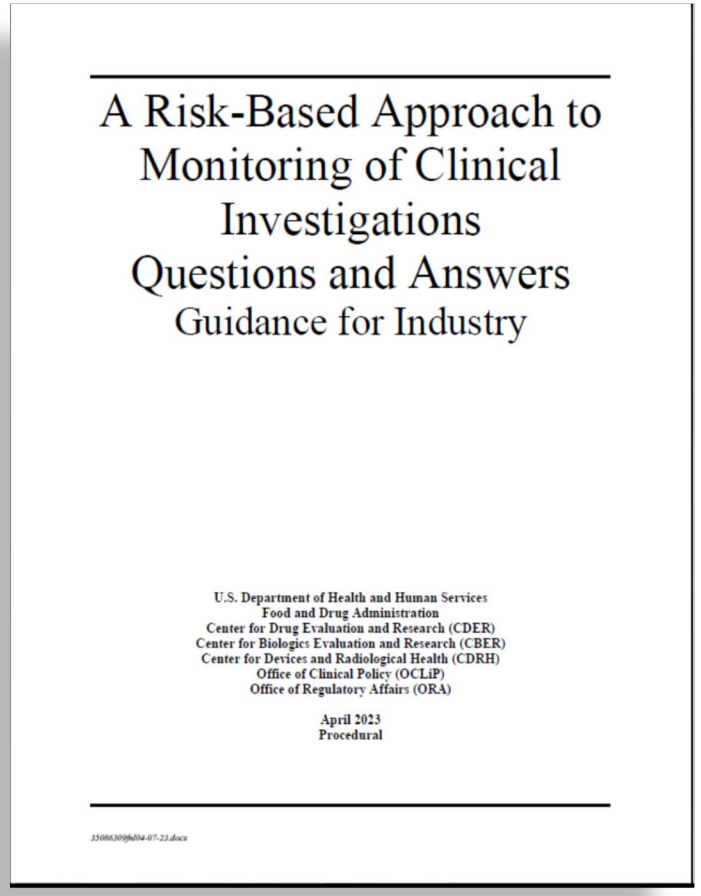
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Office of Good Clinical Practice (OGCP)
Office of Regulatory Affairs (ORA)

August 2013
Procedural

OMB Control No. 0910-0014
Current expiration date available at https://www.reginfo.gov
(Search ICR and enter OMB control number 0910-0014)
See additional PRA statement in section VII of this guidance.

Published 2013

https://www.fda.gov/media/116754/download



A Risk-Based Approach to Monitoring of Clinical Investigations Questions and Answers

Guidance for Industry

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 Clinical Policy (OCLiP)
Office of Regulatory Affairs (ORA)

April 2023
Procedural

Published 2023

https://www.fda.gov/media/121479/download

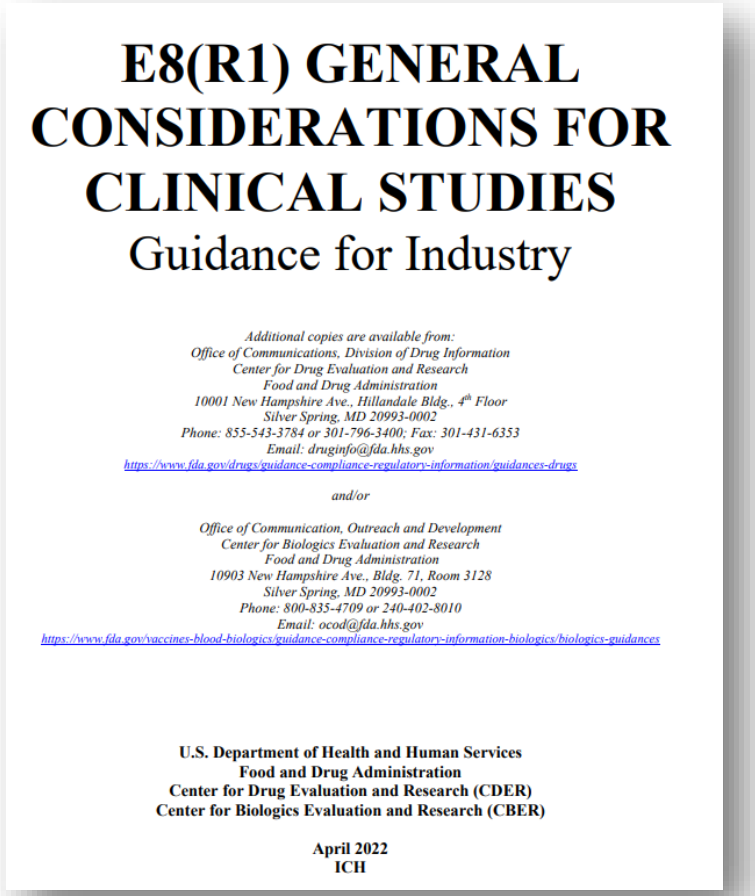
RBM Guidance Key Concepts

- Oversight focused on *critical study processes and data*
  - *Risk assessments* to identify and mitigate risks – initial as well as throughout study as needed
  - Development of study-specific *monitoring plan* informed by risk assessment to manage important risks
  - Dynamic approach for *continual improvement* in trial conduct and oversight
- Promotes use of *centralized monitoring* including harnessing electronic systems and statistical assessments

RBM 2023 Q&A Guidance

- Builds on 2013 RBM guidance to provide additional recommendations to facilitate implementation of risk-based monitoring, including:
  - Risk assessments – including documentation of methods, conclusions, and implementation of initial and updated assessments
  - Monitoring approach – tailored to investigation and site-specific risks, including tailored approach to source data verification as needed
  - Monitoring plan content – including plan for adjusting monitoring activities based on findings
  - Monitoring results – addressing and communicating results including adjustments to monitoring plan and/or protocol for additional risks identified during the conduct of the study

ICH Guidelines



E8(R1) GENERAL CONSIDERATIONS FOR CLINICAL STUDIES

Guidance for Industry

Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

and/or

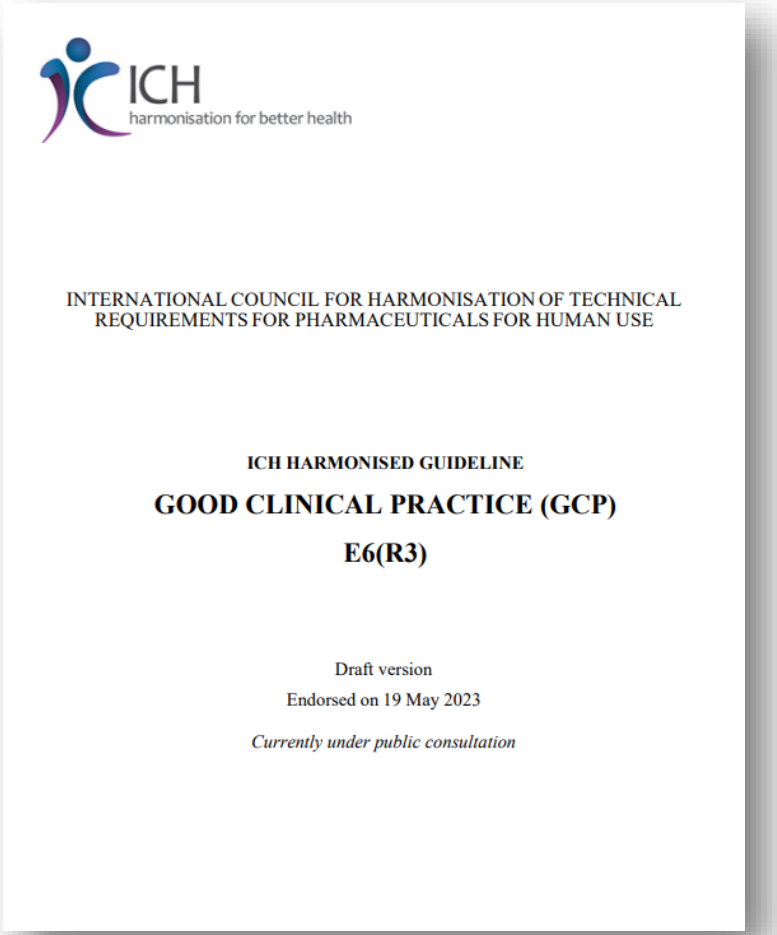
Office of Communication, Outreach and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010
Email: ocod@fda.hhs.gov
https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances

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)

April 2022
ICH

Published 2022

https://www.fda.gov/media/157560/download



ICH
harmonisation for better health

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

GOOD CLINICAL PRACTICE (GCP)

E6(R3)

Draft version

Endorsed on 19 May 2023

Currently under public consultation

Draft, published 2023

https://www.fda.gov/media/169090/download

ICH E8(R1): General Considerations for Clinical Studies

- Describes quality of a clinical study as *fitness for purpose*
- Emphasizes *designing quality into the clinical study* to ensure protection of participants and generation of reliable and meaningful results
- Focuses on the identification and review of *critical to quality factors* at the time of design and planning of the study, as well as throughout the study conduct, analysis, and reporting
- Entails the management of important risks using a *risk proportionate approach*

ICH-E6: Global Good Clinical Practice Standard for Clinical Trial Conduct

E8 clinical trial design principles

↕

E6 GCP clinical trial conduct principles

- **E6: Good Clinical Practice (GCP) – 1996**
- **E6 (R2) –2016**
- **E6 (R3) – Public consultation in 2023**

ICH E6 is unique as the only harmonized guideline among the global regulatory community for clinical trial conduct

Background to E6(R3) Renovation

Gap analyses & Engagements

- **Literature review**
  - **Open letter to EMA & ICH**
  - **Published articles**
  - **Relevant guidelines**
- **Clinical Trial Transformation Initiative's (CTTI) survey and interviews**
- **Engagements with academic experts**
- **Engagements with the community at large via public meetings**

Updated open Letter to EMA & ICH: From ~~2~~ 5 research organisations and an international consortium of ~~84~~ 119 health researchers in ~~19~~ 22 countries

Signatories listed at end:
Original signatories of 31st January letter shown in black with new signatories of this letter shown in red

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Stakeholders' views on the most and least helpful aspects of the ICH E6 GCP guideline and their aspirations for the revision of ICH E6(R2)

Carrie Dombeck[a,b], Teresa Swezey[a,b], Annemarie Forrest[a], Pamela Tenaerts[a], Amy Corneli[a,b,c,*]

[a] Clinical Trials Transformation Initiative, Duke University, Durham, NC, USA
[b] Department of Population Health Sciences, Duke University School of Medicine, Durham, NC, USA
[c] Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9468347/pdf/main.pdf

Initial Takeaways from Feedback and Comments on ICH-E6(R2)

- E6 is widely applied to non-regulatory clinical trials, despite being intended for trials supporting regulatory submission (also confusion about the applicability to observational studies)
- Concerns that funders' "reflexive requirement" stifles non-regulatory research, especially in under-resourced areas (concerns that the guideline doesn't support a risk-based approach, and that it has a "one-size-fits-all" approach to trials and is written as an inspection check list…)
- Concerns about ability to meet all GCP requirements in different situations (e.g., during public health emergencies)

ICH E6(R3): Good Clinical Practice

- Intended to provide a flexible and modern framework to support innovate approaches
  - Clinical trials should be designed to protect the rights, safety and well-being of participants and assure reliability of results
  - Clinical trial designs and conduct should be proportionate to the risks and the importance of the data being collected
  - Trial designs and conduct should minimize unnecessary complexity and burden

What is unique about E6(R3) development process

- **Engagement** with academic stakeholders
- New approaches to **enhance transparency** (published draft principles in April 2021 and conducted two workshops)
- Robust **training program** will be developed with use-cases focused on trial designs that may encounter difficulties in the application of GCP guidelines

What is unique about E6(R3) structure and content?

- **New structure** to provide clarity and better readability
  - Principles to remain relevant as technology, methods, and trial design evolve
  - Annexes and appendices (better flow and a strategy intended to enable easier and faster updates in the future)

- Focused **scope**

- Language to **facilitate innovations** in trial design & technology
  - Enabling DCTs and PoCs among other design elements
  - Expect the use of DHTs, healthcare infrastructure, and other design elements & tools to recruit/retain, capture data, monitor, and to analyze results

What is unique about E6(R3) structure and content?

Overall themes

- Set a foundation for **practical/feasible** expectations around the responsibilities from sponsor and investigator in a digital ecosystems
  - **Proportionality and risk-based** approaches with a focus on quality while keeping the emphases and focus on **participants' safety** and **reliability of trial results**
  - **Thoughtfulness** in the design and conduct with QbD, and RBQM at the core
- Encourage **a fit-for-purpose** approaches
- **Incorporate learning** from innovative trial designs and lessons from public health emergencies/pandemics
- Encourage a focus (of efforts and resources) on what matters most (areas of relevance to **participants safety and results reliability**)
- Encourage trial **registration** and **result reporting**
- Encourage **better informed consent process**

What is next?

Work Started on E6(R3) Annex-2

The proposed development of Annex 2 will include additional considerations on how GCP principles may be applied across a variety of trial designs and data sources, where applicable. This will include:

1- Decentralised elements, where some or all trial-related activities occur at locations other than traditional clinical trial sites, such as patient homes, mobile trial units, or local clinics, and data collection may occur remotely.
2- Pragmatic elements, reflecting trials that closely resemble routine clinical practice.
3- Real-world data (RWD) sources[2], for example, the use of registries, electronic health records (EHR), hospital data, pharmacy and medical claims data or wearables.

It will take a village –

E6 and E8 provide a foundation for robust design and responsive and proportionate GCP expectations. *However*, **guidelines alone** are not adequate in addressing all scenarios and evolving innovations. We still to:

- **Collaborate** on **implementation and capacity building,** which are critical with increasingly global clinical trials
- **Develop** **responsive and accessible training** with the global community in mind
- **Avoid** an **all-or-nothing approach** to innovative designs and technologies – thoughtfulness is needed (hybrid designs utilizing fit-for-purpose tools and technologies may be most efficient)

Conclusion

- FDA is committed to supporting the modernization of the clinical trial enterprise
- QbD and RBQM are integral components to implementation of proportionate and risk-based quality management approach
- ICH E6(R3) is intended to support innovations and advance efficiencies in trial design and conduct, while ensuring safety and quality

Questions?

FDA, Office of Medical Policy
CDEROMP@fda.hhs.gov

A VIEW FROM EUROPE
CLINICAL TRIAL GCP RENOVATION – BUILDING QUALITY INTO DESIGN AND RISK PROPORTIONATE APPROACHES TO TRIAL DESIGN AND CONDUCT

SESSION 1: RISK-BASED APPROACHES TO BUILDING QUALITY INTO THE DESIGN AND CONDUCT OF CLINICAL INVESTIGATIONS - REGULATORY PERSPECTIVES OF QBD AND RBM

Fergus Sweeney, Clinical Trial Expert, Retired

31 January 2024

Building Quality into the Design and Conduct of Clinical Studies:
Integrating Quality by Design (QbD) and Risk-Based Monitoring (RBM) Approaches

Robert J. Margolis, MD, Institute for Health Policy and US Food and Drug Administration

Hybrid Public Meeting • National Press Club • Washington, DC

- Views expressed are those of the speaker only.
- Speaker has no conflict of interest and is retired.

ICH E family of guidelines – need to be read together

E8 General Considerations for Clinical Studies

Design and analysis:

E4 Dose-Response Studies
E9 Statistical Principles for Clinical Trials
E10 Choice of Control Group in Clinical Trials
E17 Multi-Regional Clinical Trials
In preparation E20 Adaptive Clinical Trials

Conduct and reporting:

E3 Clinical Study Reports
E6 Good Clinical Practice

Safety reporting:

E1 Clinical Safety for Drugs used in Long-Term Treatment
E2A - E2F Pharmacovigilance
E14 Clinical Evaluation of QT
E19 Safety Data Collection

Populations:

E5 Ethnic Factors
E7 Clinical Trials in Geriatric Population
E11 - E11A Clinical Trials in Pediatric Population
E12 Clinical Evaluation by Therapeutic Category
In preparation E21 Inclusion of Pregnant and Breastfeeding Individuals in Clinical Trials

Genetics/genomics:

E15 Definitions in Pharmacogenetics / Pharmacogenomics
E16 Qualification of Genomic Biomarkers
E18 Genomic Sampling

E8 Fundamental design elements

- Study population
- Intervention
- Control group
- Response variable
- Methods to reduce bias
- Statistical analysis

Described in the protocol together with the study objectives, study type, and data sources which should be finalized before start of study (ICH E6)

E8 clinical trial design principles

E6 GCP clinical trial conduct principles

ICH E8 (R1) – General Considerations on Clinical Studies

General Principles
Protection of participants
Scientific approach to design, conduct and analysis
Patient input into drug development

Quality by Design & Critical to Quality Factors

Drug development planning

Study design, conduct & reporting

Critical to Quality Factor examples

Annex – Study Types

ICH E8 Quality of a clinical study

- 2.2 Scientific Approach in Clinical Study Design, Planning, Conduct, Analysis, and Reporting

- **Quality** of a clinical study is …. **fitness for purpose**.
- **The purpose** of a clinical study is to **generate reliable information** to **answer the research questions** and **support decision making** while **protecting** study **participants**.
- The **quality** of the **information** generated should therefore be **sufficient to support good decision making**.
- **Quality by design** .. to ensure that the **quality of a study is driven proactively** by **designing quality** into the study **protocol** and **processes**…
    - use **prospective**, **multidisciplinary approach** to promote the quality of protocol and process design,
    - in a manner **proportionate to the risks** involved,
    - **clear communication** of how this will be achieved.

ICH E8
2.3 Patient Input into Study Design

- **Consulting with patients and/or patient organisations** in the **design, planning** and **conduct** of clinical studies **helps to ensure that all perspectives are captured.**
- **Patients' views can be requested on all phases** of drug development.
- **Involving patients at the early stage of study design** is likely to **increase trust** in the study, **facilitate recru**itment, and **promote adherence**, which **should continue throughout** the duration of the study.
- Patients also **provide their perspective of living with a condition**, which contributes to the determination of **endpoints that are meaningful to patients, selection of the right population, duration of the study, and use of the right comparators.**
- This ultimately supports the **development of medicines that are better tailored to patients' needs.**

Involving Stakeholders in ICH GCP Renovation.

Two-fold approach:

Stakeholder engagement during the **drafting process**:

- *Global Workshop on ICH E8 – Oct 2019, Washington, D.C.*
- *ICH E6 GCP stakeholder engagement plan*
- *Regional Workshops on ICH E6 revision in June 2020*
- *Regional Representatives of academic research engage with the ICH E6 GCP Expert Working Group – ongoing since August 2020*

Stakeholder engagement is **built into** the revised ICH E8 **guideline**:

- *Foresees involvement of patients in study planning, anchored among E8 principles*
- *Stipulates including stakeholders across disciplines in study planning & design for identifying what is critical to study quality*

Stakeholder involvement is very informative and enriching

- it leads to better guidance and better clinical trial designs, with greater buy in of stakeholders to the process and the results

ICH E8
3.2 Critical to Quality Factors

- *A **basic set of factors relevant to ensuring study quality** should be identified for each study. **Emphasis** should be given to **those** factors **that stand out as critical to study quality.***

- ***..critical** because, if **their integrity were to be undermined** …the reliability or ethics of **decision-making would also be undermined.***

- ***..determine the risks that threaten their integrity,** the probability and impact of those risks and to **decide whether they can be accepted or should be mitigated.***

- ***Perfection** in every aspect ..is **rarely achievable or .. only** .. achieved by use of resources **..out of proportion to the benefit obtained. …study procedures should be proportionate to the risks inherent in the study and the importance of the information collected.”***

Section 3.3 Approach to Identifying the Critical to Quality Factors

- 3.3.1 Identifying attributes whose integrity is fundamental to study quality via: **Establishing a Culture that Supports Open Dialogue:**
  - *.. **values and rewards critical thinking and open dialogue** about quality ..beyond sole reliance on tools and checklists.*
- 3.3.2 **Focusing on Activities Essential to the Study:**
  - *.. essential to the reliability and meaningfulness of study outcomes for patients..safe, ethical conduct .. for study participants. Consider whether n**onessential activities may be eliminated…to simplify conduct…improve efficiency…targe critical areas.***
- 3.3.3 **Engaging Stakeholders in Study Design:**
  - *..best informed by **input from a broad range of stakeholders, including patients and treating physicians**. It should be ope to **challenge by subject matter experts and stakeholders from outside**, as well as within, the sponsor organisation.*
- 3.3.4 **Reviewing Critical to Quality Factors:**
  - ***Build on accumulated experience and knowledge** with **periodic review of critical to quality factors** to determine whether **adjustments to risk control mechanisms are needed, since new or unanticipated issues may arise** once the study has begun*

…to optimally align research objectives with planning, conduct and decision making by promoting flexibility instead of one-size-fits-all strategy.

ICH E8 3.1 Quality by Design of Clinical Studies

- Quality is a primary consideration in the design, planning, conduct, analysis, and reporting of clinical studies and a necessary component of clinical development programmes.
- The likelihood that a clinical study will answer the research questions while preventing important errors can be dramatically improved through prospective attention to the design of all components of the study protocol, procedures, associated operational plans and training.
- Activities such as document and data review and monitoring, where conducted retrospectively, are an important part of a quality assurance process; but, even when combined with audits, they are not sufficient to ensure quality of a clinical study.

ICH E.8 3.2 Critical to Quality Factors

- 3.2. …..The sponsor and other parties designing quality into a clinical study should identify the critical to quality factors.
- Having identified those factors, it is important to determine the risks that threaten their integrity and decide whether they can be accepted or should be mitigated, based on their probability, detectability and impact.
- Where it is decided that risks should be mitigated, the necessary control processes should be put in place and communicated, and the necessary actions taken to mitigate the risks.

7 Considerations in Identifying Critical to Quality Factors

Discussion of critical to quality factors in this guideline

Section 3: Designing Quality into Clinical Studies

The identification of critical to quality factors should be supported by proactive, cross-functional discussions and decision making at the time of study planning

Section 4: Drug Development Planning

Section 5: Design elements for Clinical studies

Section 6: Conduct and Reporting

Different factors will stand out as critical for different types of studies

In designing a study, applicable aspects such as the following should be considered to support the identification of critical to quality factors, as shown in Section 7

ICH GCP Draft Principles

- **7 Clinical trial processes, measures and approaches should be implemented in a way that is proportionate to the risks to participants and to the importance of the data collected.**
  - 7.1 Trial processes should be **proportionate to the risks inherent in the trial** and the importance of the information collected. ….
  - 7.2 The focus should be on the **risks to participants beyond those associated with standard medical care.**….
  - 7.3 **Risks to critical to quality factors should be managed prospectively** and **adjusted** when **new or unanticipated** issues arise once the trial has begun.

ICH GCP Draft Principles

- **8. Clinical trials should be described in a clear, concise and operationally feasible protocol.**
  - 8.1 A **well-designed trial protocol is fundamental** to the protection of participants and for the generation of reliable results.
  - 8.2 **The scientific objectives of any trial should be clear and explicitly stated i**n the protocol.
  - 8.3 The clinical trial **protocol** as well as the **plans or documents for the protocol execution** (e.g., statistical analysis plan, data management plan, monitoring plan) should be **clear, concise and operationally feasible.**

ICH GCP Draft Principles

9. Clinical trials should generate reliable results.

- 9.1 The quality and amount of the information generated in a clinical trial should be **sufficient to provide confidence** in the trial's results and **support good decision making.**
- 9.2 Systems and processes that aid in data capture, management and analyses, as well as those that help ensure the quality of the information generated from the trial, should be **fit for purpose**, should capture the data required by the protocol and should be implemented in a way that is **proportionate to the risks to participants** and the **importance of acquired data**. Trial processes should be **operationally feasible and avoid unnecessary complexity, procedures and data collection**. Trial processes should support the key trial objectives.
- 9.4 Computerised systems used in clinical trials should be **fit for purpose**, and factors critical to their quality should be addressed in their design or adaptation for clinical trial purposes.

Digitalisation

- Establishing Trust, Enabling Research
  - *Data provenance, validity (technical and scientific)*
  - *New data sources*
  - *Personal data protection is an enabler of research –*
    - Patients have a legal right that their privacy is protected.
    - They also have a legitimate expectation that they have access to involvement in research and to its benefits, and that their data is well used so research can answer important questions.
    - These need to be properly addressed.
  - *Complex landscape of data generation, collection and analysis, digital communication, remote visits, use of wearables, electronic informed consent*
- Need to set standards for use of digital tools and information that are universally applicable, future proof, ensure data trust and participant protection
- Support innovation and new approaches – health and medicines are complex but we should not make it complicated
- Use the opportunities and support the possibility of better clinical trials, better research and better healthcare
- Use of digital tools is progressing in healthcare as well as in CTs.

Enabling decentralised clinical trials

- Decentralised approaches to clinical trials can be used, for the right research questions, medicines and therapeutic indications - for research questions which DC approaches are capable of addressing.
- A clinical trial should deliver reliable results that can be used as the basis of decision making – the science should be addressed first, and then a determination of whether that can be addressed using DC approaches
  - *It depends……on the research question, the medicine, the therapeutic indication, requirements of the trial, need for in person contact for the tests, treatment administration and care of the participant.*
- Decentralised tools and approaches may be used singly or in combinations. The individual elements are not generally new as such, they are possible, and have been used in trials and in healthcare for a long time.
- Sponsor and investigator have clear legal roles and responsibilities.
- Take care that the role of the investigator is clear and that the medical care of the trial participant, in the context of the trial, is clearly controlled and delivered by the investigator.
- The autonomy of the trial participant needs to be respected.
- Pandemic situation is a clear use case.

Enabling Centralised monitoring

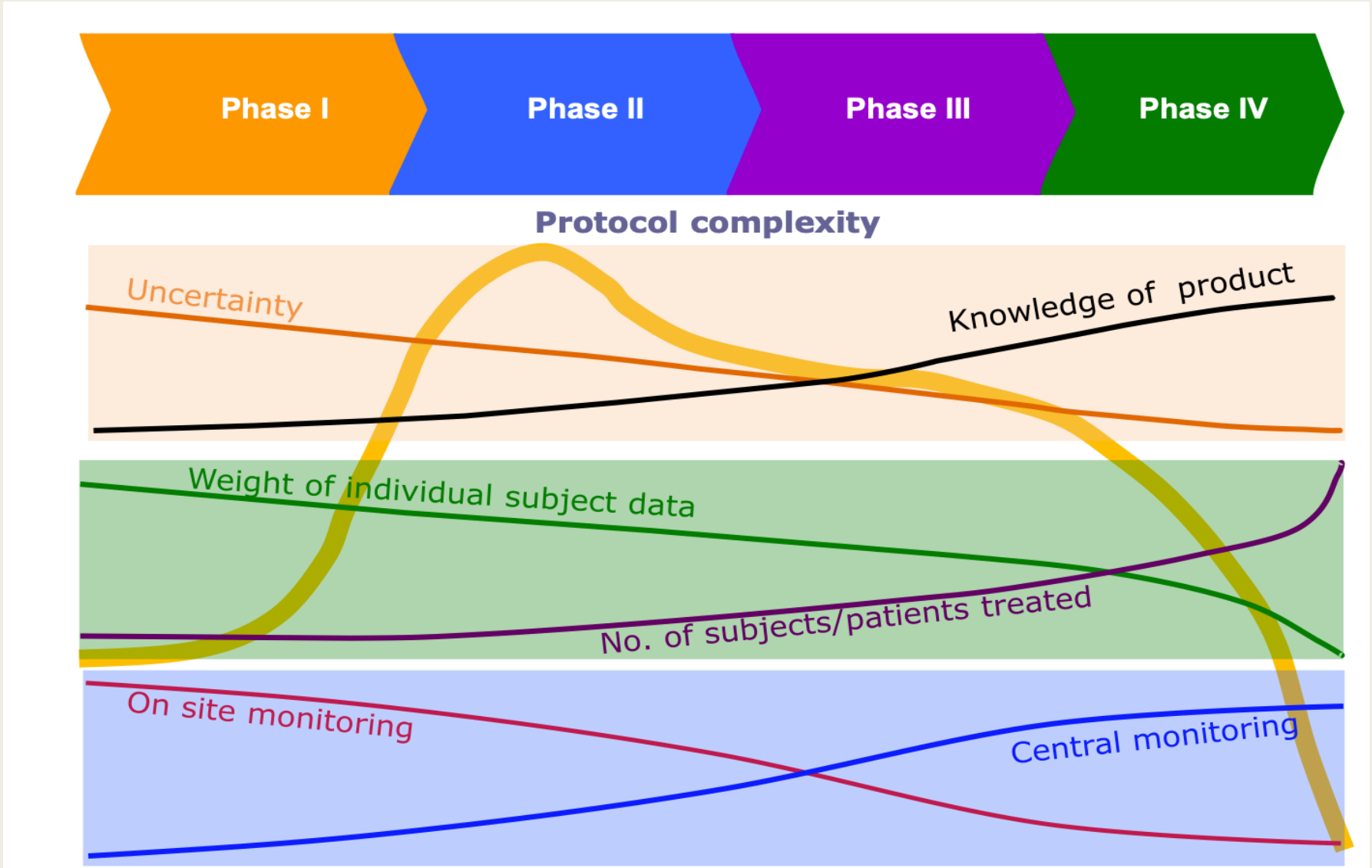
- Digitalisation and new trial designs and analytical methods open great opportunities for centralised monitoring and its use in the control, monitoring and data management of clinical trials

- ICH E6 *3.11.4 Monitoring*
  - *The aim of monitoring is to ensure the participants' rights, safety and well-being and the reliability of trial results as the trial progresses. Monitoring is one of the principal quality control activities.*
  - *Monitoring involves a broad range of activities including, but not limited to communication with investigator sites, verification of the investigator and investigator site staff qualifications and site resources, training and review of trial documents and information using a range of approaches including source data review, source data verification, data analytics and visits to institutional facilities undertaking trial-related activities. Some of these monitoring activities may be conducted by different methods and persons with different roles.*
  - *The monitoring approach should consider the activities and services involved, including decentralised settings, and be included in the monitoring plan.*
  - *The sponsor should determine the appropriate extent and nature of monitoring, base on identified risks. Factors such as the objective, purpose, design, complexity, blinding, number of trial participants, investigational product, current knowledge of the safety profile and endpoints of the trial should be considered*

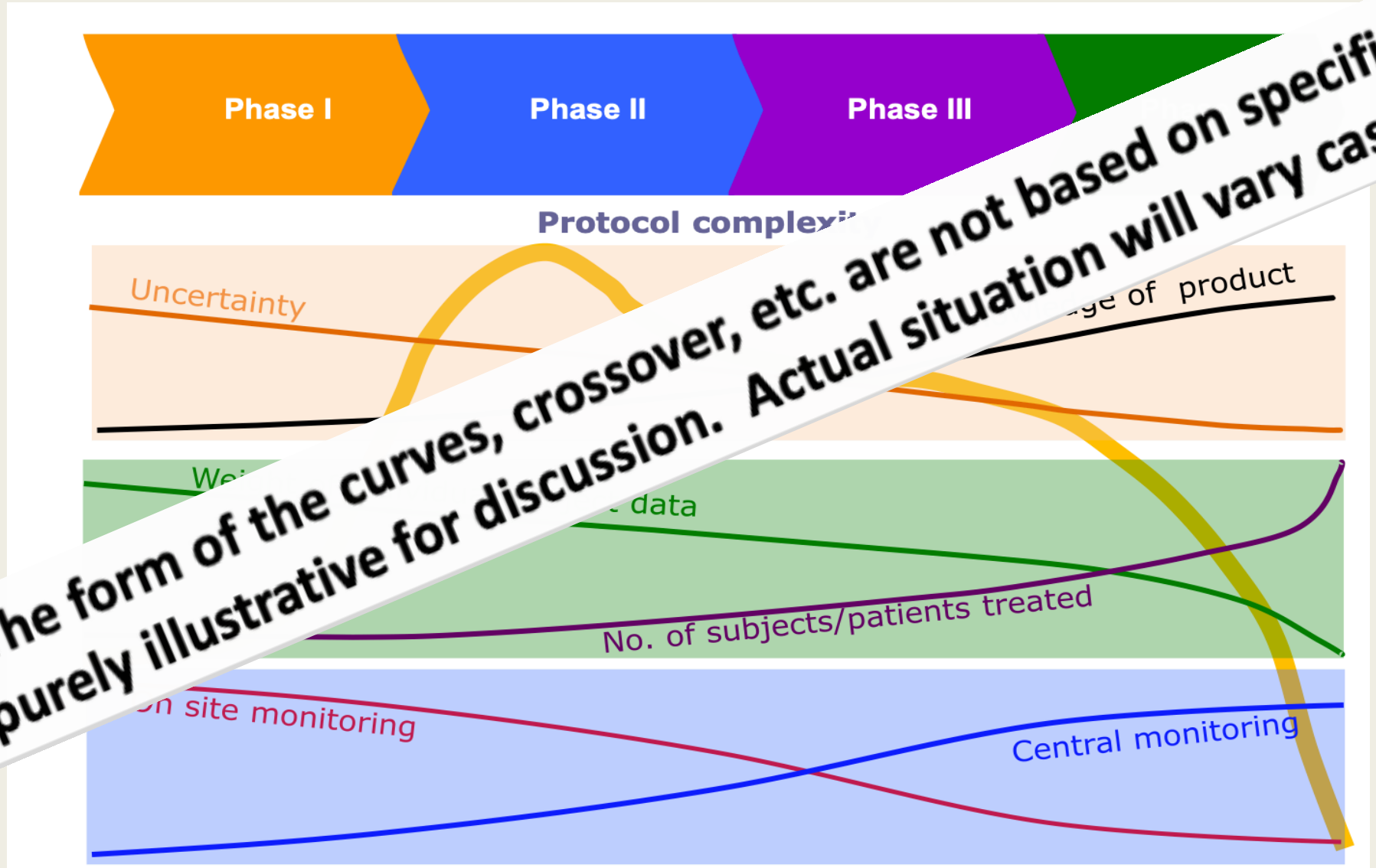
Enabling Centralised monitoring

- 3.11.4.2 Centralised Monitoring
  - (a) Centralised monitoring is an evaluation of accumulated data, performed in a timely manner, by the sponsor's qualified and trained persons (e.g., medical monitor, data scientist/data manager, biostatistician).
  - (b) Centralised monitoring processes provide additional monitoring capabilities that can complement and reduce the extent and/or frequency of site monitoring or be used on its own. Use of centralised data analytics can help identify systemic or site-specific issues, including protocol non-compliance and potentially unreliable data.
  - (c) Centralised monitoring may support the selection of sites and/or processes for targeted site monitoring.

ICH E8 4. Drug development planning builds on knowledge acquired throughout the investigational process to reduce levels of uncertainty as the process moves from target identification through non-clinical and clinical evaluation.



ICH E8 4. Drug development planning builds on knowledge acquired throughout the investigational process to reduce levels of uncertainty as the process moves from target identification through non-clinical and clinical evaluation.



N.B.: The form of the curves, crossover, etc. are not based on specific data.
This is purely illustrative for discussion. Actual situation will vary case by case.

Accelerating Clinical Trials in the EU

ACT EU is a joint initiative of HMA/European Commission/EMA

to **transform the EU clinical research environment**

in support of medical innovation and better patient outcomes.

Support the conduct of **large, multinational trials** with specific support for:

- SME, academia and Health Technology Assessment bodies (HTAs); and
- Trials which address unmet needs, rare diseases & medicines for public health crises
- Large randomised trials, platform trials, point of care trials…

Facilitate **coordinated scientific advice** to support trial authorisation, marketing authorisation & the medicine lifecycle

Ensure **a unified European approach** for trial processes and strategic matters at the international level

Engage all stakeholders to deliver inclusive patient-oriented medicines development and delivery across populations

Multi Stakeholder Platform established in 2023

Everyone involved in the conduct of clinical trials should read and understand these guidelines.

Change the way we all work – don't add more to the status quo.

Change Management is the greatest challenge

– adjusting behaviors, attitudes – away from preconceived ideas and interests – and on to a new, better, way of working.

The greatest achievements will be by those who embrace new approaches and seek to make them work – there is no regulatory impediment per se.

- "Perfection is achieved not when there is nothing more to add but when there is nothing left to take away" *Antoine de Saint-Exupéry*
- "Everything should be made as simple as possible but not simpler" *Albert Einstein*

Thank you – any questions?

Contact:

Fergus Sweeney

fergusIsweeney@icloud.com

Join at
slido.com
#QBD

Moderated Discussion and Audience Q&A

Moderator:

Jacqueline Corrigan-Curay,

US Food and Drug Administration

We Are Taking A Break…
Our Program Will Resume 10:45 am ET

Learn more about our upcoming events and workshops.

Visit healthpolicy.duke.edu/events

Session 2: Optimizing Study Design and Setting the Stage for Efficient Study Conduct Through QbD: Successes and Challenges

Moderator: **Morgan Hanger,** Clinical Trials Transformation Initiative

Speakers:

Kenneth Getz, Tufts Center for the Study of Drug Development

Mokash Sharma, Bristol Myers Squibb

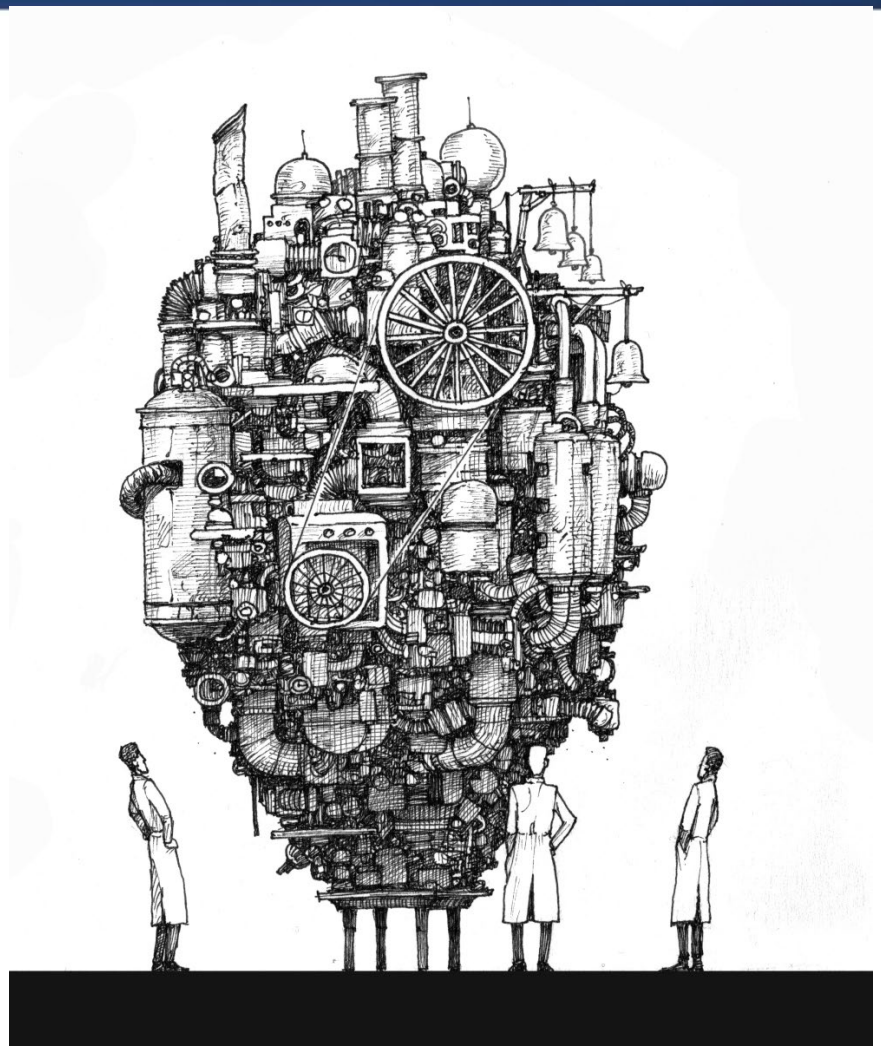
Sameera Ibrahim, Bristol Myers Squibb

Eda Baykal-Caglar, Michael J. Fox Foundation

Leslie Sam, Leslie Sam and Associates, LLC

Sabrina Comic-Savic, Population Health Partners

Optimizing Study Design and Setting the Stage for Efficient Conduct through Quality by Design



Ken Getz, MBA

Executive Director and Research Professor

Tufts CSDD

Tufts University School of Medicine

January 2024

Tufts Center for the Study of Drug Development

TUFTS UNIVERSITY

About the Tufts Center for the Study of Drug Development

Center History: 48-year-old Independent, globally-focused, academic group based within Tufts University School of Medicine (Boston).

Mission: Conduct robust, data-driven assessments and analyses to inform drug development stakeholders committed to optimizing quality, performance, efficiency and economics.

Communities Served: Congress, the National Academies of Science, Foundations, Industry, Regulatory Agencies (e.g., FDA, EMA) EFPIA, PhRMA, BIO, DOD, NIH, CTTI, Capital Markets.

Protocol Design and its impact on Clinical Trial Performance

Protocol Design Practice

Phase III Pivotal Trials *(Means)*	2010	2020	10-Year Change
Total Endpoints	13	22	69.2%
Total Eligibility Criteria	34	30	-11.8%
Total Procedures	187	263	40.6%
Total Countries	9	15	66.7%
Total Investigative Sites	65	104	60.1%
Procedures per Visit	11	13	18.2%
Total Patients Randomized	597	632	5.9%
Total Data Points Collected	929,203	3,560,201	283.2%

Source: Tufts CSDD

Protocol Performance Experience

Phase III Pivotal Trials	10-year Change
Initiation Duration (approval to FPFV)	27.2%
Enrollment Duration (FPFV – LPLV)	36.9%
Closeout Duration (LPLV to DBL)	16.3%
Total Substantial Amendments	113.3%
Drop-Out Rates	105.1%

Source: Tufts CSDD

Protocol 'Simplification' and Authoring Tools

Percent of Procedures	Sponsors	FDA Reviewers
Core	48%	18%
Required & Standard	34%	56%
Non-Core	18%	26%
Highly Relevant	38%	43%
Somewhat Relevant	50%	7%
Not Very Relevant	6%	0%
Not at All Relevant	6%	50%

Smith and Getz. Case study assessment on the rationale for, and relevance of, non-core protocol data. TIRS. December 2023

Creating 'Line of Sight' between endpoints and procedures

1. **SPIRIT Checklist**

   http://www.spirit-statement.org/wp-content/uploads/2013/01/SPIRIT-Checklist-download-8Jan13.pdf

2. **TransCelerate Common Protocol Template**

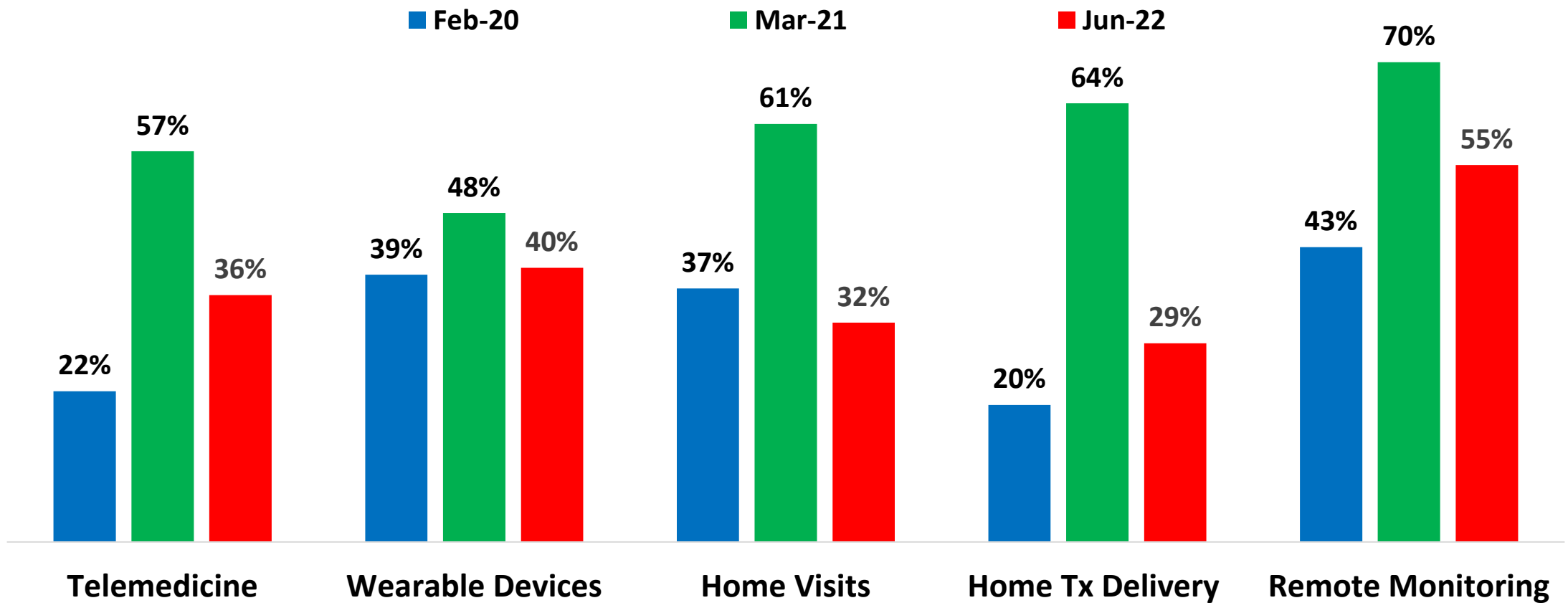
   http://www.transceleratebiopharmainc.com/assets/common-protocol-template/

3. **Metrics Champion Consortium – Protocol Design scoring Tool**

   www.metricschampion.org

Remote and Virtual Solutions Adoption

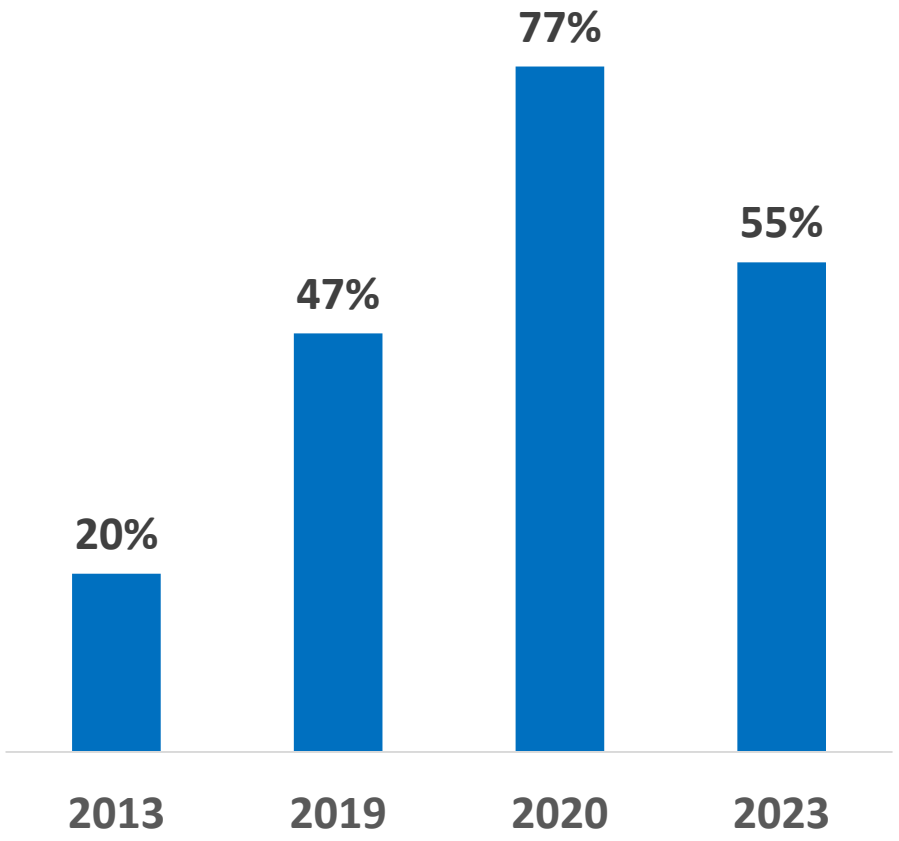
Percent of Companies Report Deploying



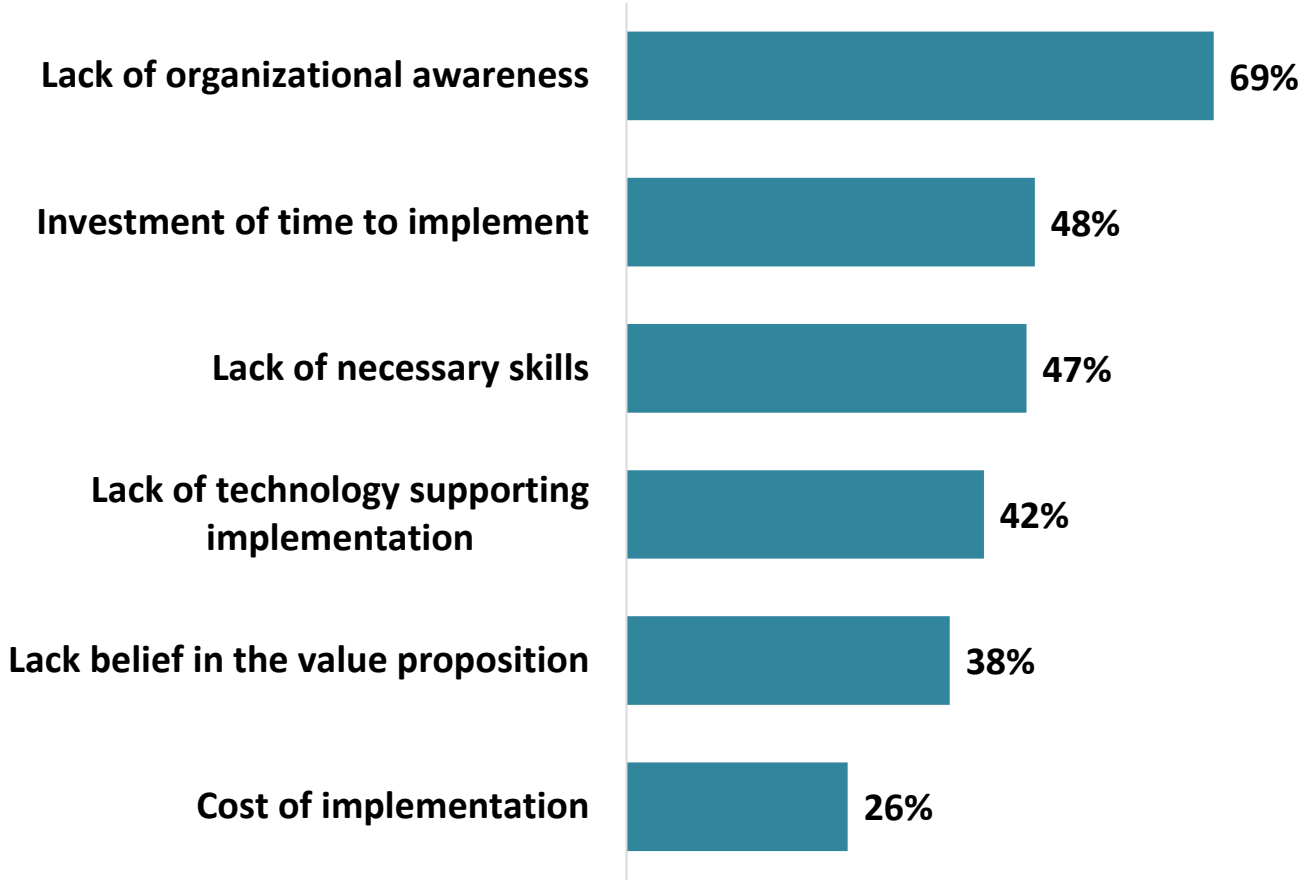
Source: Tufts CSDD; N=54 individual companies

Adoption and Application of RBM/RBQM

Adoption of RBM/RBQM

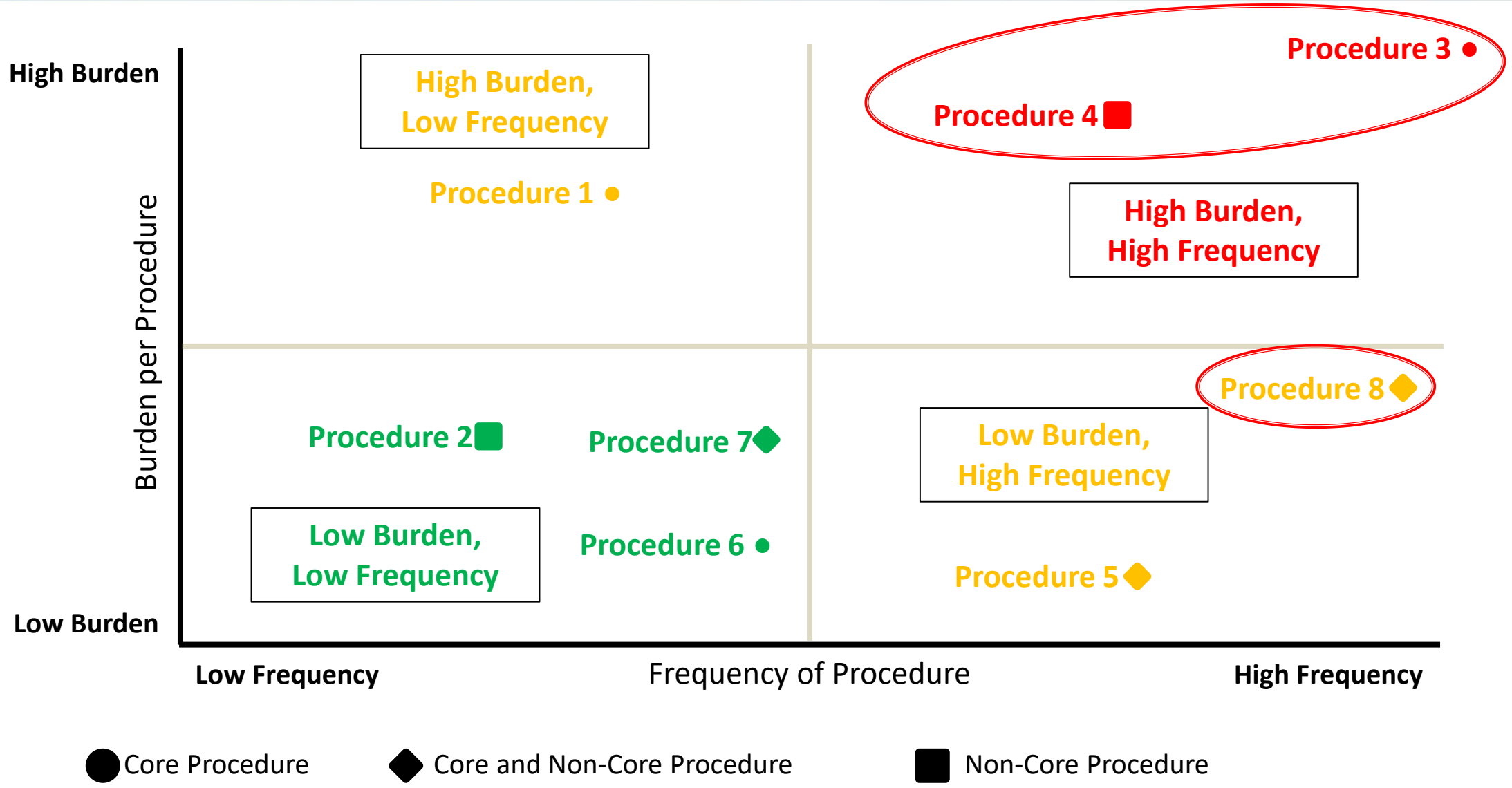


Top Reported Adoption Barriers



Sources: MCC 2015 (n=45 sponsors and CROs); ACRO 2019 and 2020 (n= 7 CROs); Tufts CSDD 2023 (n=125 sponsors)

Assessing Participation Burden in Draft Protocols



Soliciting Patient Input in Protocol Designs

Phase III Protocol *(Means)*	No Patient Input	Use of Patient Advisory Board
Total endpoints	21.2	15.0
Total eligibility criteria	33.6	26.7
Total distinct procedures	38.5	34.4
Total planned visits	19.7	18.0
Protocol Approval to FPFV (actual as percent of plan)	90.2%	4.6%
FPFV to LPLV (actual as percent of plan)	43.4%	-6.2%
LPLV to Database Lock (actual as percent of plan)	21.5%	-16.5%

Source: Tufts CSDD, 2021; Pilot study n = 40 protocols

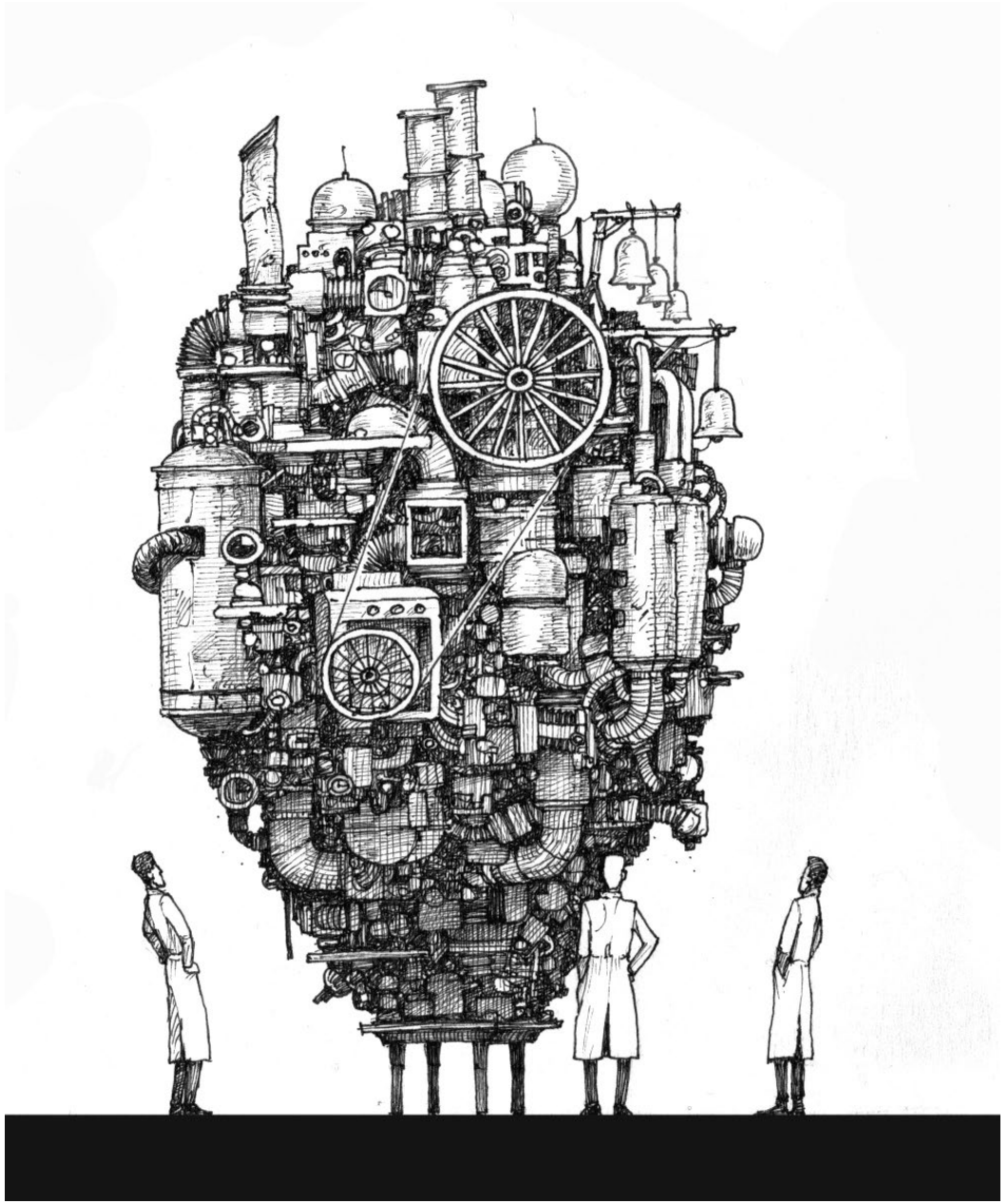
Thank You!

Ken Getz

Executive Director and Research Professor

Tufts CSDD, Tufts University School of Medicine

617-636-3487, Kenneth.getz@tufts.edu



Select Tufts CSDD Manuscripts on Protocol Complexity

- ***Assessing the Impact of Protocol Design Change on Clinical Trial Performance*. AJT 2008**
- ***Variability in Protocol Design Complexity by Phase and Therapeutic Area*. DIJ 2011**
- ***Measuring the Incidence, Causes and Repercussions of Protocol Amendments*. DIJ 2011**
- ***Quantifying the Magnitude and Cost of Collecting Extraneous Protocol Data*. AJT 2013.**
- ***New Governance Mechanisms to Optimize Protocol Design*. TIRS 2013.**
- **Therapeutic Area Variability in the Collection of Data Supporting Protocol Endpoints and Objectives*. Future Science Clinical Investigations* 2014**
- ***The Impact of Protocol Amendments on Clinical Trial Performance and Cost*. TIRS 2016**
- ***Trends in Clinical Trial Design Complexity*. Nature Review Drug Discovery, 2017**
- ***Protocol Design Variables Highly Correlated with, and Predictive of, Clinical Trial Performance*. TIRS, 2022**
- ***Protocol Design and Performance Benchmarks by Phase and by Disease Subgroups*, TIRS 2022**

FDA / Duke Margolis Institute for Health Policy Workshop

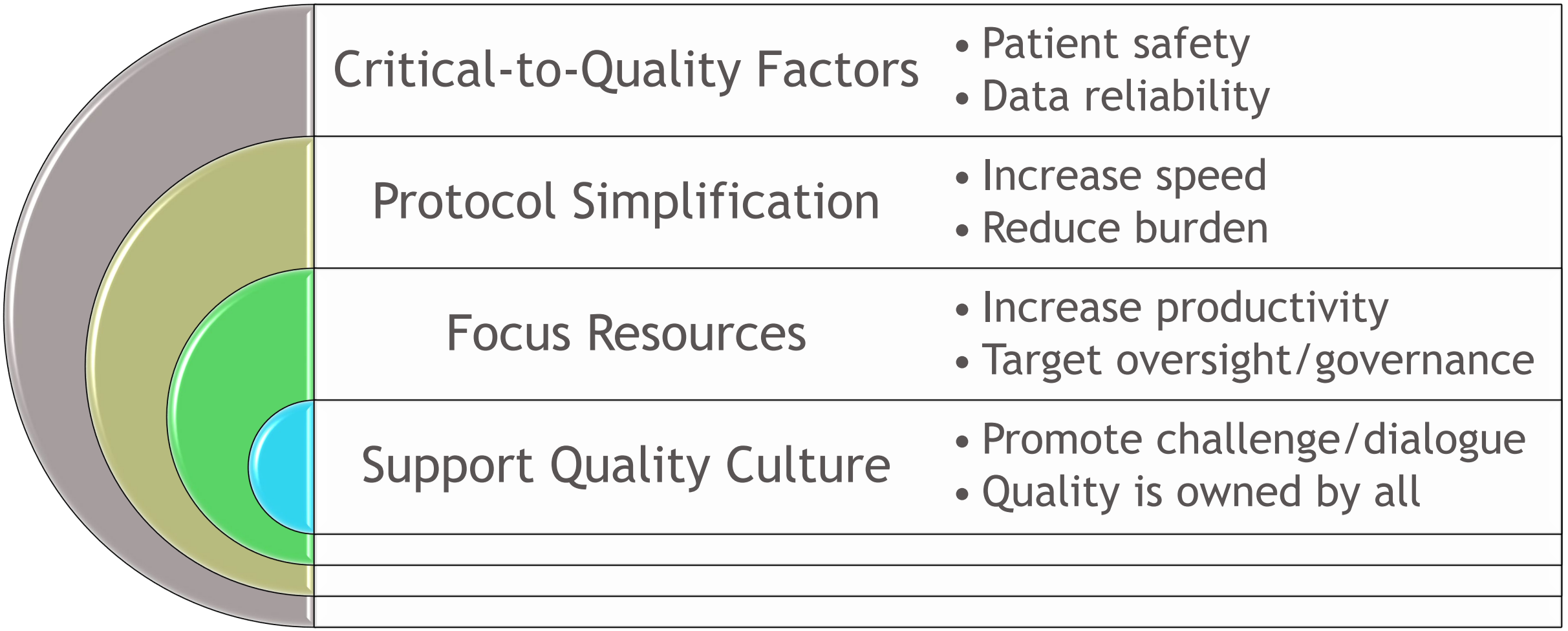
Optimizing Study *Design* and Setting the Stage for Efficient Study *Conduct* Through Quality by Design: *Successes & Challenges*

January 31, 2024

Mokash Sharma, SVP, Head of Global Development Operations
Sameera Ibrahim, Sr. Director, Strategy & Governance Excellence, R&D Quality

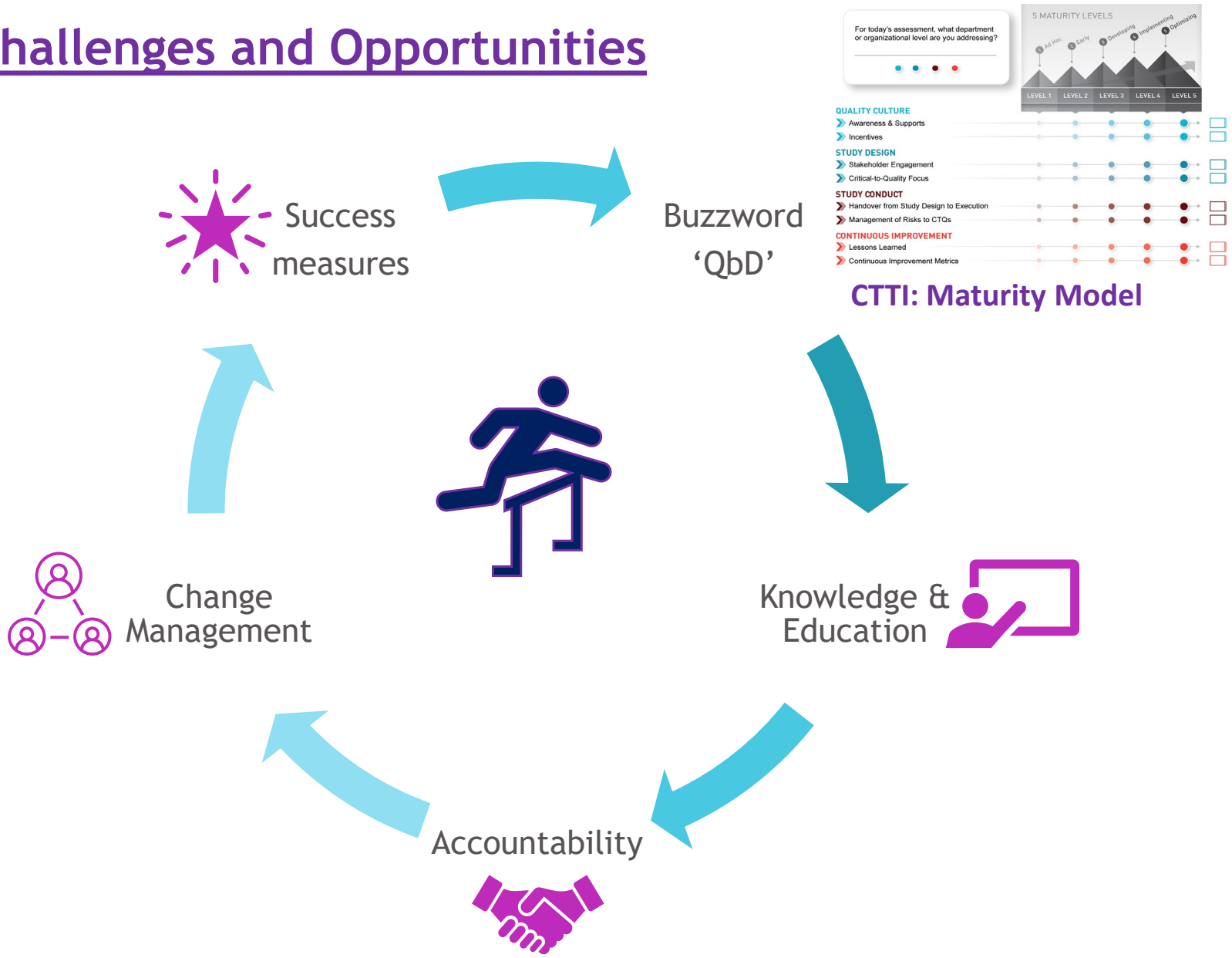
Bristol Myers Squibb™

Optimizing Study Design through Quality by Design (QbD)



Challenges and Opportunities

Working Smarter



CTTI: Maturity Model

*Cultivate QbD as a **practical** & **intuitive** approach rather than a **bureaucratic burden** on teams*

STOP & THINK!

Critical to Quality factors - Idiopathic Pulmonary Fibrosis (IPF) study

Working Smarter

Ref: Case Study Published on CTTI Website: CTTI Implementation Case Studies (ctti-clinicaltrials.org)

CtQ FACTORS	PROTOCOL ADJUSTMENTS
❑ Patient Safety	BP monitoring
❑ Protocol Design	Visit windows - to provide flexibility Data capture tools & cadence – to optimize output
❑ Feasibility	

CRITICAL DATA

- ✓ **Safety data**
- ✓ **Efficacy endpoint**

CtQ Data Lifecycle

Operational & Study set-up

GCP Compliance, QC & QA

Critical to Quality factors - Oncology study

Working Smarter

DRAFT PROTOCOL

STAKEHOLDER INPUT

TOOLS

CtQ FACTORS

PROTOCOL ADJUSTMENTS

CRITICAL DATA

- ❑ Patient Safety — Local lab
- ❑ Protocol Design — Time & Events – support patient compliance
- ❑ Third party engagement

- ✓ **Central pathology review**
- ✓ **Patient retention**

CtQ Data Lifecycle

Operational & Study set-up

GCP Compliance, QC & QA

Risk Management- centered on CTQ factors | Future State

Goals in Action: The Michael J. Fox Foundation for Parkinson's Research Quality by Design Journey

Eda Baykal-Caglar, PhD
Director of Patient Engagement

The Michael J. Fox Foundation for Parkinson's Research

THE MICHAEL J. FOX FOUNDATION
FOR PARKINSON'S RESEARCH

Here. Until Parkinson's Isn't.

- Launched in 2000 by actor Michael J. Fox
- Vision seeks a world without Parkinson's disease
- Strategic research vision centered on *enabling* advances in disease *definition*, *measurement* and *treatment* across the Parkinson's disease *progressive journey*
- Global strategic funder and facilitator: more than $1 billion deployed to Parkinson's disease research and drug development
- Accelerating cures by connecting community: people with Parkinson's, care providers, researchers, industry, regulators, payers, policy-makers, strategic partners and other visionary philanthropists

THE MICHAEL J. FOX FOUNDATION
FOR PARKINSON'S RESEARCH

MJFF Guiding Principles

Important considerations shape and amplify the impact of our programmatic actions

People-centered Research

Programs that matter to people with PD

Leveraged Resources

Programs use available resources to reduce duplication

Diversity, Equity and Inclusion

Programs integrate DEI solutions

External Validation

Programs include external advisors to validate strategy

Open and Reproducible Science

Programs promote collaboration and replication

Impactful Partnerships

Programs bridge like-minded partners

THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

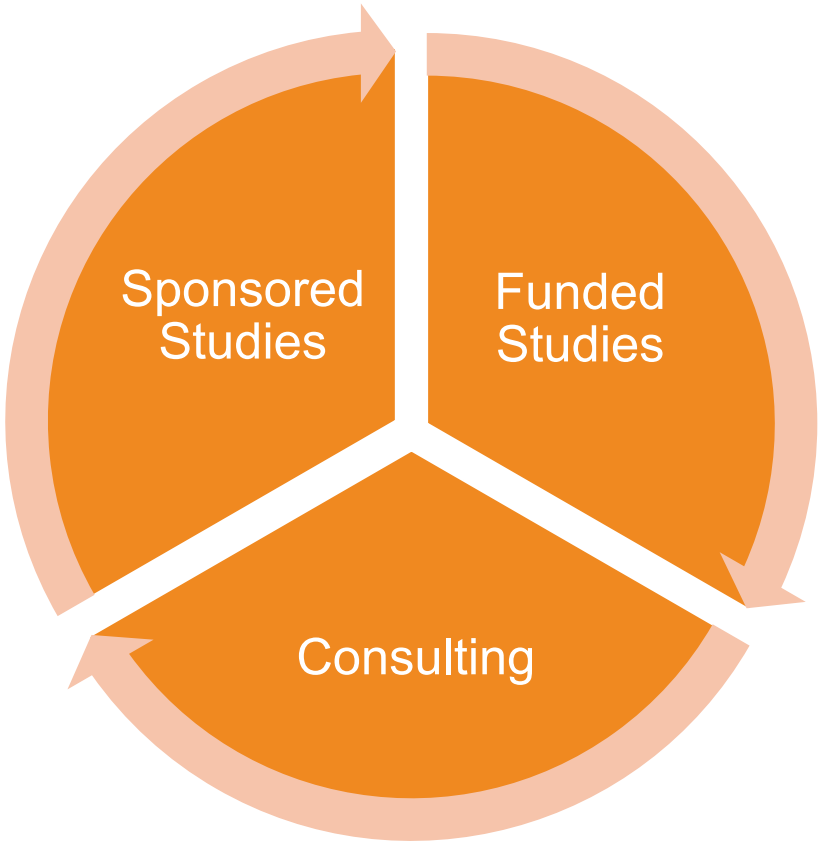
Our Commitment to Patients

MJFF was founded by a person with Parkinson's disease.

We assess all potential projects through a patient-focused lens so everything we do is driven by the many unmet needs of Parkinson's patients today.

QbD Work at MJFF

Learnings from patients — through surveys, advisory boards, etc. — and the field information to help our QbD recommendations.



Leveraging Available Samples & Planned Procedures

Reduce participant burden for invasive procedures

- Landmark observational Parkinson's Progression Markers Initiative (PPMI) study has initiated **dual enrollment SOPs** with some interventional trials
- A new biomarker is available but requires lumbar puncture or skin biopsy. There is potential to **leverage samples/results from other studies or commercial access** for eligibility considerations.

Remote Data Capture

Reduce clinical burden and collect relevant data

- PPMI is leveraging an online portal: Additional questionnaire data and frequency of data collection for the study

- PPMI app to collect RWD: SOA updated to condense the frequency of active tasks required after feedback from *patients.*

Concierge Experience

Ease Travel Burden and Make It Possible for Lower SES Volunteers

- **Travel services recommendations:**

PPMI provides travel services and we emphasize it in conversations with other stakeholders.

- **Non-traditional reimbursements:**

Pet boarding, paid caregiver for loved ones

QbD Template *	
Protocol Design	Eligibility Criteria
	Randomization
	Data Parsimony
	Endpoints
	Participant Input
Feasibility	Study & site feasibility
	Recruitment
	Retention
Participant Safety	Informed Consent
	Signal Detection& Safety Reporting
	Stopping Rules
Study Conduct	Training
	Data Management& Monitoring
	Statistical Analysis
Study Reporting	Dissemination of Results

Funded Studies

- Since 2018 more than 200 reviews
- Most of the feedback has been on feasibility and protocol design
- Working on improved implementation process.

** CTTI Principles Document*

Consulting with Industry

Field-wide learnings

- 30 consultations to pharma/biotech; 15 unique companies consulted in 2023.
    - Protocol review
    - Material reviews
    - Recruitment
- Connections to MJFF audience

Challenges and Opportunities

- **Challenges**
  - Training on QbD process
  - Measuring the impact:
    - reduced protocol amendments,
    - meeting recruitment and retention targets
    - increased participant diversity
- **Opportunities**
  - Assess and improve our approach.
  - Build multidisciplinary expertise across the organization.
  - Continue to share our experience with others through consulting, presentations, and publications.

Thank You!

Join at
slido.com
#QBD

Moderated Discussion and Audience Q&A

Moderator:

Morgan Hanger,

Clinical Trials Transformation Initiative

Break for Lunch

Workshop will resume at **1:25 p.m. ET**

Session 3: Translating QbD Principles to Risk-Proportionate Oversight Including RBM: Successes and Challenges

Moderator: **Laurie Muldowney,** US Food and Drug Administration

Speakers:

Nicole Stansbury, Association of Clinical Research Organizations

Patrick Nadolny, Sanofi

Michael Walega, PHUSE

Kristin Stallcup, Takeda

Steve Young, CluePoints

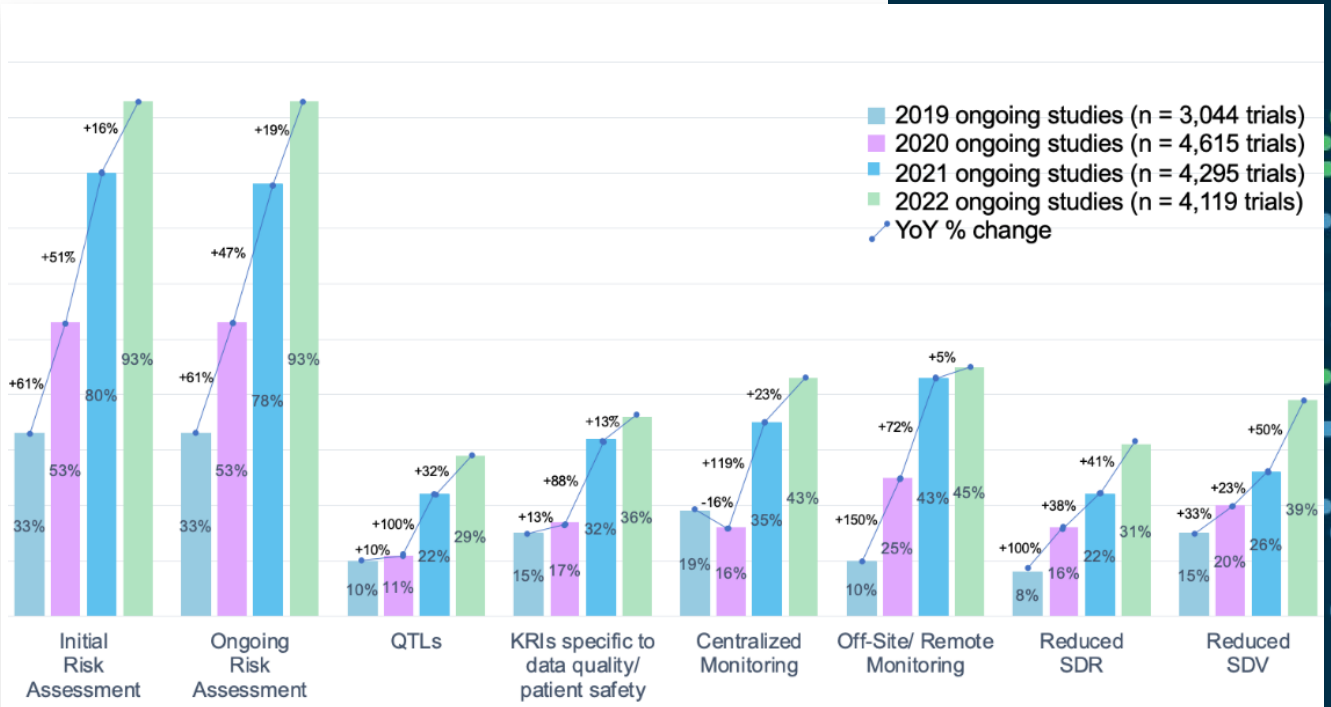
Introduction & About ACRO

- Presenter: Nicole Stansbury, SVP Global Clinical Operations, Premier Research
- ACRO is a trade association that brings together the world's leading CROs and technology companies. ACRO's mission is to **advocate as the collective voice of innovative clinical research and technology organizations** to regulators and policymakers, educating stakeholders and shaping policies that foster efficient, effective and safe conduct of clinical research.
- ACRO hosts several committees including:
  - Risk Based Quality Management (RBQM) Working Group
  - Decentralized Clinical Trials (DCT) Working Party
  - Diversity & Inclusion (D&I) Committee
  - And others

premier research
Built for Biotech℠

ACRO's Landscape Survey

- Goals of RBQM
  - More **effective** ways of monitoring
    - Protect patient rights, welfare and safety (trends, outliers)
    - Ensure data integrity (trends, outliers)
  - More **efficient** ways of monitoring
    - Prioritize critical data and critical process
    - Faster detection of errors/issues leading to faster remediation
    - Location and availability of resources to perform monitoring
    - Reduce the extent or frequency of onsite monitoring (travel, site burden)
  - Not intended to eliminate **all** errors



Source: Adams, A., Adelfio, A., Barnes, B. et al. Risk-Based Monitoring in Clinical Trials: 2021 Update. Ther Innov Regul Sci 57, 529–537 (2023). https://doi.org/10.1007/s43441-022-00496-9

Complete landscape survey results can be found at www.acrohealth.org

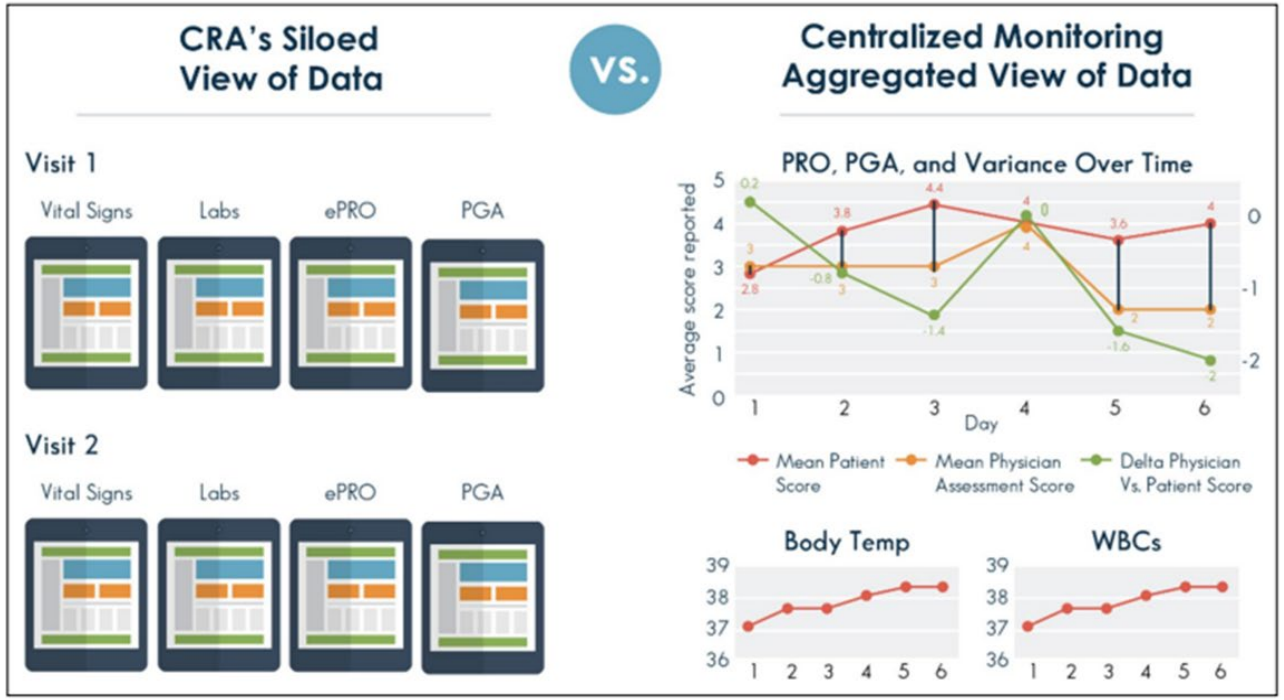


Fig. 4 *Monitoring of Siloed Data Versus Centralized Monitoring with Visualization of Aggregated Data*. Centralized monitoring allows clearer identification of trends or aberrations in clinical trial data compared with monitoring by a CRA, who has a more siloed view of the data

Central Monitoring Data Visualizations Can Significantly Improve Patient-Level Monitoring

Source: Adams, A., Adelfio, A., Barnes, B. et al. Risk-Based Monitoring in Clinical Trials: 2021 Update. Ther Innov Regul Sci 57, 529–537 (2023). https://doi.org/10.1007/s43441-022-00496-9

Complete landscape survey results can be found at www.acrohealth.org

Different Central Monitoring Strategies

	Front Line Defenses (Advanced Edit Checks)	Standard KRIs (Site Level Outliers)	Patient Level Data Reviews (Patient Profiles)	Study Level Data Reviews (Safety, Efficacy Focused)	Quality Tolerance Limits (Custom-Study-Level KRIs)
Critical Process Focus	Low	Low	High	Low	Low
Critical Data Focus	High	Low	Mod	High	High
Technology Requirements	Mod	Mod	High	Mod	Mod
Implementation Difficulty	Mod	Mod	Mod	Low	Mod
Efficiency Gains	High	Mod	High	Low	Low
Cost to Implement	Mod/Low	Low	Mod	Mod/High	Mod
Benefits	Can catch issues across data in different source systems	Identifies poor performing sites for focused attention	Reduces the need for frequent onsite monitoring (reports at a site level can look very similar to IMVs in content)	Identifies trends and allows for remediation “in stream”	Can highlight issues that must be mitigated for the study to be successful

Different SDR/SDV Sampling Strategies

	Data Point	Form/Procedure	Patient Visit	Patient	Combos - Pt and Proc; Pt and Pt Visit
Critical Process Focus	Low	Mod	High	Mod	Varies
Critical Data Focus	High	High	Mod	Low	Varies
Technology Requirements	High	High	Mod	Low	High
Implementation Difficulty	High	Mod	Low	Low	Mod
Efficiency Gains	Low	Low	Mod	High	Mod
Cost to Implement	High	High	Low	Low	Mod

Different SDR/SDV Sampling Strategies (cont.)

	Data Point	Form/Procedure	Patient Visit	Patient	Combos - Pt and Proc; Pt and Pt Visit
Benefits	Works on any study	Works on any study	Works on any study, except those with very few visits per patient	Works only on studies with a large volume of patients/site	Maximum efficiency on very large trials or large trials with very few visits/patient (e.g. vaccine)
Risks	Distracts from critical process and validation of data vs verification of transcription; encourages "reverse monitoring"	Distracts from critical process and validation of data vs verification of transcription; encourages "reverse monitoring", but to a lesser extent than data point verification	Encourages focus on critical process and critical data within a visit: Eligibility, Dosing, AE reporting, endpoint collection and the relationships to protocol compliance	Encourages focus on critical process and critical data within a visit: Eligibility, Dosing, AE reporting, endpoint collection and the relationships to protocol compliance	Encourages focus on critical process and critical data within a visit: Eligibility, Dosing, AE reporting, endpoint collection and the relationships to protocol compliance

Keys to RBQM Oversight

1. Data aggregation and availability/access (ensuring APIs/data transfers are timely)
2. Look for a simple-to-follow plan and clear roles/responsibilities across organizations
3. Ensure procedures are in place
4. Be careful not to break important “connections” (CM and CRA, CM and DM, etc.) with outsourcing decisions
5. Confirm compliance to plan
6. Assess data issues rationally:
   - Systemic issue?
   - Significant impact to patient safety?
   - Significant impact to trial integrity?

Ensuring Data Quality during disruptions

Can Quality by Design and Disruptions co-exist?

Patrick Nadolny

Global Head, Clinical Data Management, sanofi

Chair of the Board, Society for Clinical Data Management (SCDM)

Quality Mindset & Culture

ICH
harmonisation for better health

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

GENERAL CONSIDERATIONS FOR CLINICAL STUDIES

E8(R1)

Final version

Adopted on 6 October 2021

ICH E8 (R1)

Nov 2021

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of ICH regions.

3.3.1 Establishing a Culture that Supports Open Dialogue

Creating a culture that values and rewards **critical thinking** and open, proactive dialogue about what is critical to quality for a particular study or development programme, going beyond sole reliance on tools and checklists, is encouraged. Open dialogue can facilitate the development of innovative methods for ensuring quality.

Inflexible, "one size fits all" approaches should be discouraged. Standardised operating procedures are necessary and beneficial for conducting good quality clinical studies, but study specific strategies and actions are also needed to effectively and efficiently support quality in a study.

Traditional RBQM process is assessing and mitigating known risks (e.g., RACT)

Scientific **Operational**

- **Umbrella** design with risks of unblinding when using multiple routes of administration
- **Basket** design collecting multiple endpoints with risk of complex CRF and data variability
- **Adaptive** design with data integrity risks when changing data collection set-up mid-study
- **DCT** studies with multiple way of getting the same data per patient's choices (On-site, telemedicine)

- Risk Assessment also includes risks from **feasibility outcomes** (Study, Country & Site Level)
  - E.g., Deviation from SOC (Country Level) or Naive Sites (Site Level)

Assessment outcome includes **Avoidable** and **Unavoidable** risks

- De-risk avoidable (e.g., Eliminating complex secondary or tertiary data requirements in Protocol)
- Plan monitoring solutions for unavoidable risks (e.g., firewalls for risks of unblinding)

What about risk you cannot anticipate (e.g., Disruptions: Natural Disasters, etc.) **?**

- Quality Process by Design (have a process as resilient as possible to disruption)
  - Pro-active readiness for avoiding being 100% on a reactive mode if it happens

What is Data Quality?

ICH E6 (R1)

June 1996

Integrity of Clinical Data

Reliability of Trial Results

ICH E6 (R2)

Nov 2016

Data integrity

Data is managed the right way

Meets ALCOA + Good Documentation Practice standards

Attributable
Legible
Contemporaneous
Original
Accurate

+

Complete
Consistent
Enduring
Available

The controls required for integrity do not necessarily guarantee the quality of the data generated.

MHRA GxP Data Integrity 2018

Data quality

Data is credible and reliable

Fit for purpose, scientifically plausible, and reliable

High-quality data may be defined as data strong enough to support conclusions and interpretations equivalent to those derived from error-free data. INSTITUTE OF MEDICINE 1999

The assurance that data produced is exactly what was intended to be produced and fit for its intended purpose. This incorporates ALCOA. MHRA GxP Data Integrity 2018

"**fitness for purpose** … in relation to health research, policy making, and regulation and that the data reflect the reality, which they aim to represent"

EMA - Data Quality Framework for EU medicines regulations 2023

Controlling **data integrity** and **ensuring quality** to provide **reliable trial results**

FDA Public Health Emergencies Guidance

Resiliency

Considerations for the Conduct of Clinical Trials of Medical Products During Major Disruptions Due to Disasters and Public Health Emergencies

Guidance for Industry, Investigators, and Institutional Review Boards

This guidance is for immediate implementation.

FDA is issuing this guidance for immediate implementation in accordance with 21 CFR 10.115(g)(2). Submit one set of either electronic or written comments on this guidance at any time. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*. For questions regarding this document, contact (CDER) Office of Medical Policy, CDEROMP@fda.hhs.gov, 301-796-2500.

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)
Oncology Center of Excellence (OCE)
Office of Clinical Policy (OCLiP)

Sep 2023

Disasters and **P**ublic **H**ealth **E**mergencies (PHEs) have the potential to cause major disruptions in the conduct of clinical trials for medical products. Such events can include (but are not limited to) **hurricanes, earthquakes, military conflicts, infectious disease outbreaks,** or **bioterrorist attacks**. FDA is issuing this guidance to provide general considerations to assist sponsors, institutional review boards (IRBs), and clinical investigators in assuring the **safety of trial participants, maintaining compliance with good clinical practice (GCP), and minimizing risks to trial integrity during disasters** and PHEs that may lead to major disruption of clinical trial conduct and operations.

Case Study – Challenges

Major disruptions in the conduct of clinical trials

Disruption	Recent disruptive events and examples of their impacts	Magnitude
 **Natural Disasters**	**Earthquake in Turkey (2023)** *Sites no longer or partially operational (Loss of Source Data, Loss of IMPs, Missed Critical Visits, etc.)* *Lost to Follow-Up Patients* *Death: Patients, Site & Sponsor Personnel typically at **the time of the event*** *Low likelihood of recovery for some sites (Need to enroll new patients to secure study power)*	**Local** Impacted Turkey
 **Conflicts**	**War in Ukraine (2022)** *Sites Closed or Destroyed in Ukraine (Loss of Source Data, Loss of IMPs, Missed Critical Visits, etc.)* *Lost to Follow-Up Patients* *Death: Patients, Site & Sponsor Personnel typically **until the end of the conflict*** *Low likelihood of recovery for some sites (Need to enroll new patients to secure study power)* ***Patients and Site Personnel leaving Ukraine*** ***New Sites in neighbor countries to welcome exiled patients** (How to access to Source data from Ukrainian site?)* *Borders Closed (Preventing IP Distribution)* *Enrollment Stopped in some countries*	**Regional** Impacted Ukraine, Russia & Neighbor Countries (E.g., Belarus and Georgia)
 **Infectious disease outbreaks**	**COVID (2020)** ***Lockdowns** (Incl. Patients, Sponsor and Site Personnel unavailable)* ***Different Timing & Severity of outbreaks across countries*** *Borders Closed (Preventing IP Distribution)* *Death: Patients, Site & Sponsor Personnel **spread through the pandemic (Ends varying by country)*** ***Business Models unprepared** (e.g., Off-shore physical data processing hubs with no remote back-up)*	**Global** Impacted the World Outbreak & Disease control varied across continents & countries

Case Study – Opportunities

Designing a Quality by Design process

Disruption	Magnitude
Natural Disasters	**Local** Impacted Turkey
Conflicts	**Regional** Impacted Ukraine, Russia & Neighbor Countries (E.g., Belarus and Georgia)
Infectious disease outbreaks	**Global** Impacted the World Outbreak & Disease control varied across continents & countries

Example of useful KRIs for Cross Study Analysis

EDC
- Missing Visits
- Missing IMPs
- Missing Primary endpoints
- Missing Labs

Site's Status

CTMS
- Operational
- Non-Operational
- Partially Operational
- Unreachable

Impact on **Data Integrity** is "Factual"

First, data is needed including ways to capture how it was collected (Remote vs. On-site)

Loss of source data

No SDV, responses to Queries and/or Investigator's Signature

Missed Procedures & Visits

Increased Protocol Deviations

Confirmed vs. Unknown

Planned vs. Actual

Impact on **Data Quality** (i.e., Reliability of Trial Results) is "Contextual"

Country & Site impact relative to sample size of affected patients in a specific countries *(what if the world is affected)*

Data Variability & Loss of statistical power

Unknown end for pandemic & war *(Evolves over time. SO, cannot fully predict outcome – Can mainly Monitor Evolution)*

Session 3

Translating QbD Outcomes to Risk-Proportionate Oversight Including RBM: Successes and Challenges

Building Quality into the Design and Conduct of Clinical Studies: Integrating Quality by Design (QbD) and Risk-Based Monitoring (RBM) Approaches Workshop

FDA / Duke Margolis Institute for Health Policy

31Jan2024

Michael Walega, Bristol Myers Squibb

The PHUSE RBQM Working Group

Topics

- Introduction to PHUSE / Risk-Based Quality Management Working Group
- Adoption of RBQM – Successes and Challenges
- Reflections

Introduction to PHUSE / Risk-Based Quality Management Working Group

PHUSE / RBQM Working Group: Contributing to Industry Knowledge and Best Practices

- PHUSE
  - Industry consortium dedicated to sharing ideas, tools and standards around data, statistical and reporting technologies
- RBQM working group
  - Created in 2021
  - Currently consists of 3 projects: Centralised Monitoring Capabilities; Quality Tolerance Limits (QTL, Use and Implementation); Quality Tolerance Limits (Thresholds)
  - Participants from regulatory authorities, industry, service and software providers
- Deliverables to date
  - Central Monitoring – 2 white papers (*Centralized Monitoring: Exploring the Considerations and Challenges of Implementation; Can the Value of Centralised Monitoring Be Quantified*?)
  - QTL (Use and Implementation) – white paper to be published 1Q2024 (*Assessing the Use of Quality Tolerance Limits in the Pharmaceutical Industry*)
  - QTL: Thresholds – Publication (accepted for TIRS: *Quality Tolerance Limits: A General Guidance for Parameter Selection and Threshold Setting*)
- Evolution and scope of future activities
  - Planning underway for additional projects in RBQM space

Adoption of RBQM – Successes and Challenges

Pharma Industry Making Progress in Adoption: 2023 Survey

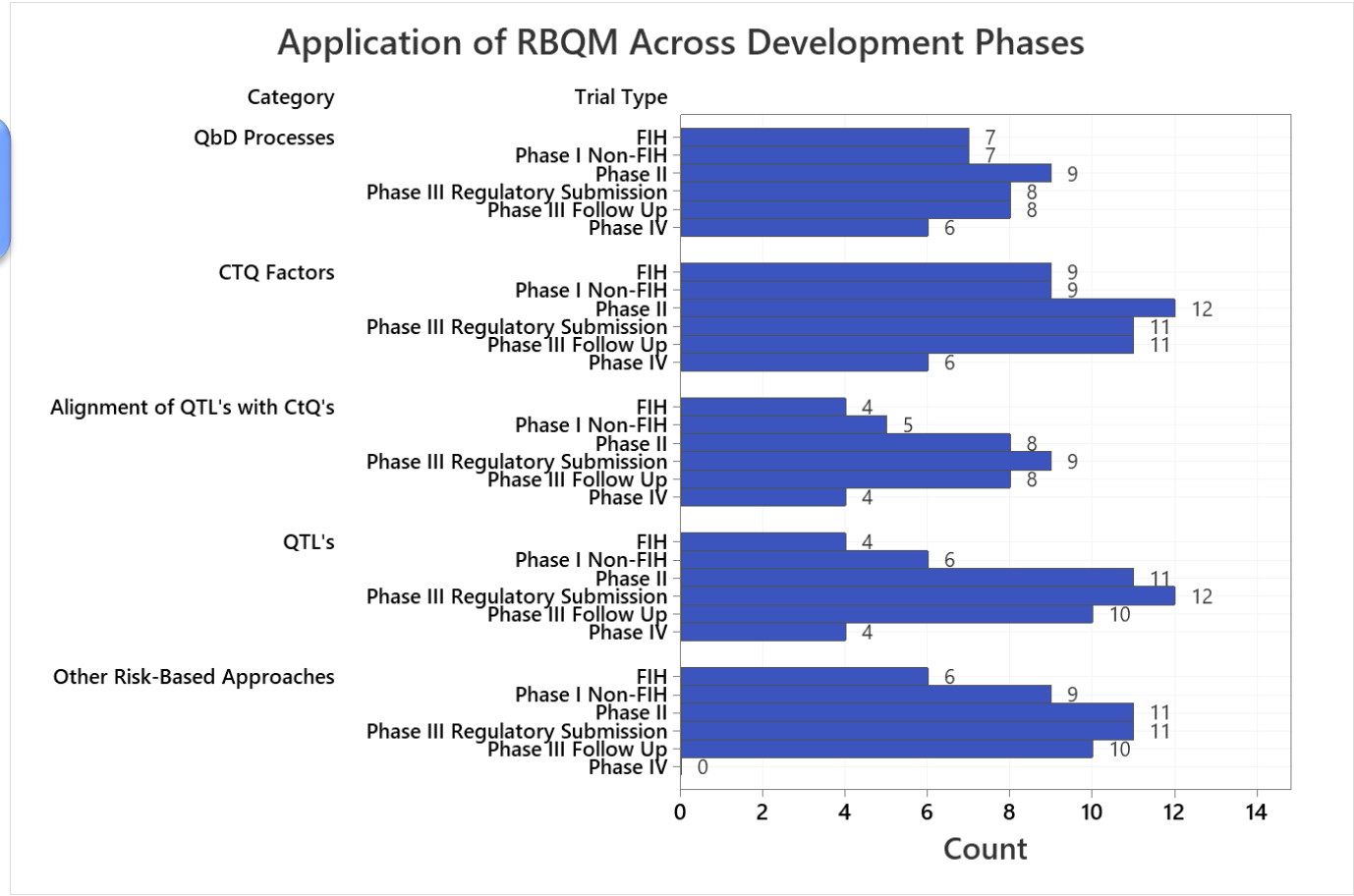
15 Respondent Organizations

= 13 Sponsors + 2 Service Providers

= 6 >200 Ongoing PI-III Trials + 4 100-200 PI-III Trials + 5 <100 PI-III Trials

QbD / CtQ Factors

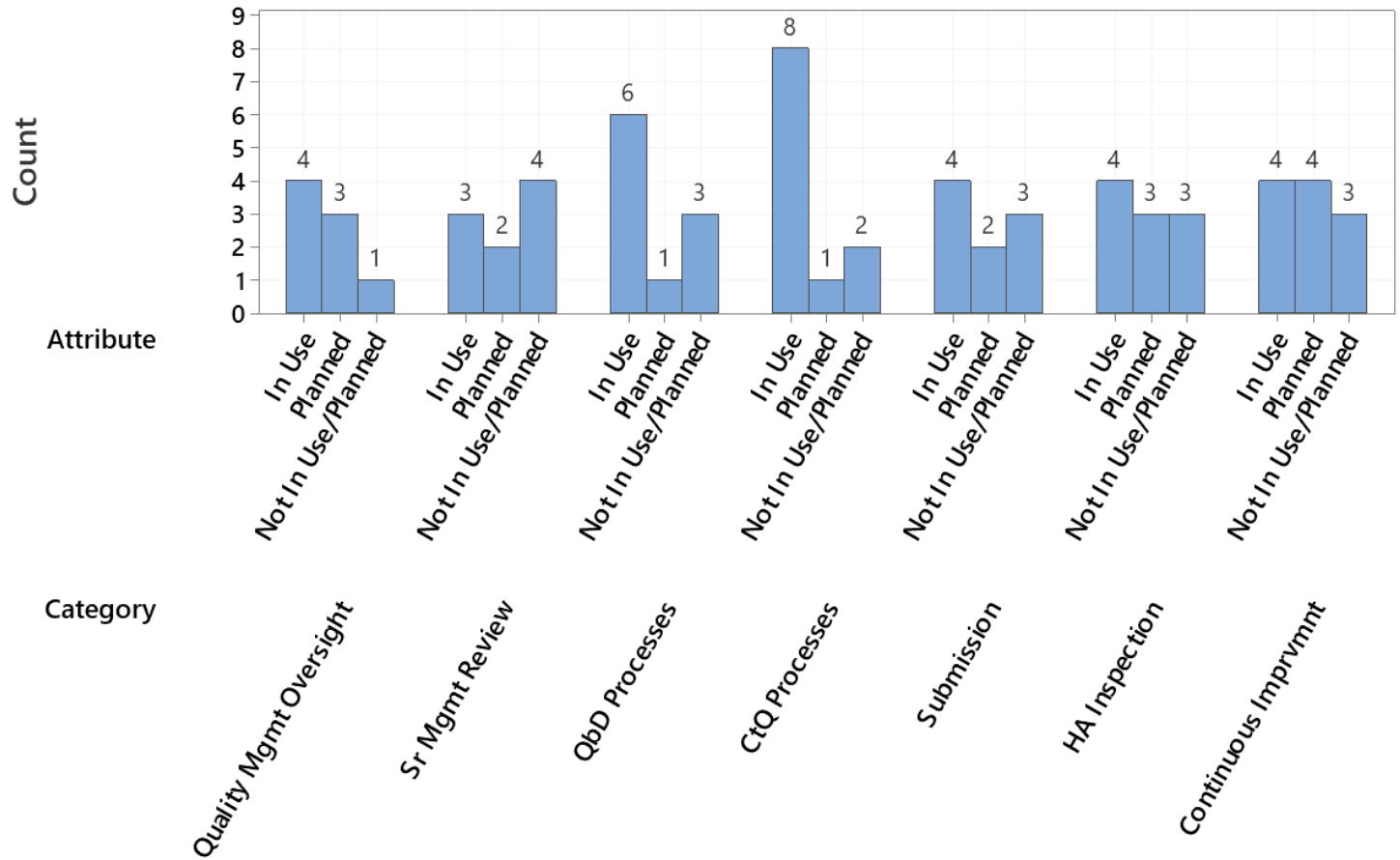
- Prevalent Phase I to IV
- Alignment to QTLs ongoing
- Implementation of QTLs less robust in early phase trials



Wider Integration of RBQM in a QMS: Work in Progress

Integration of RBQM in QMS

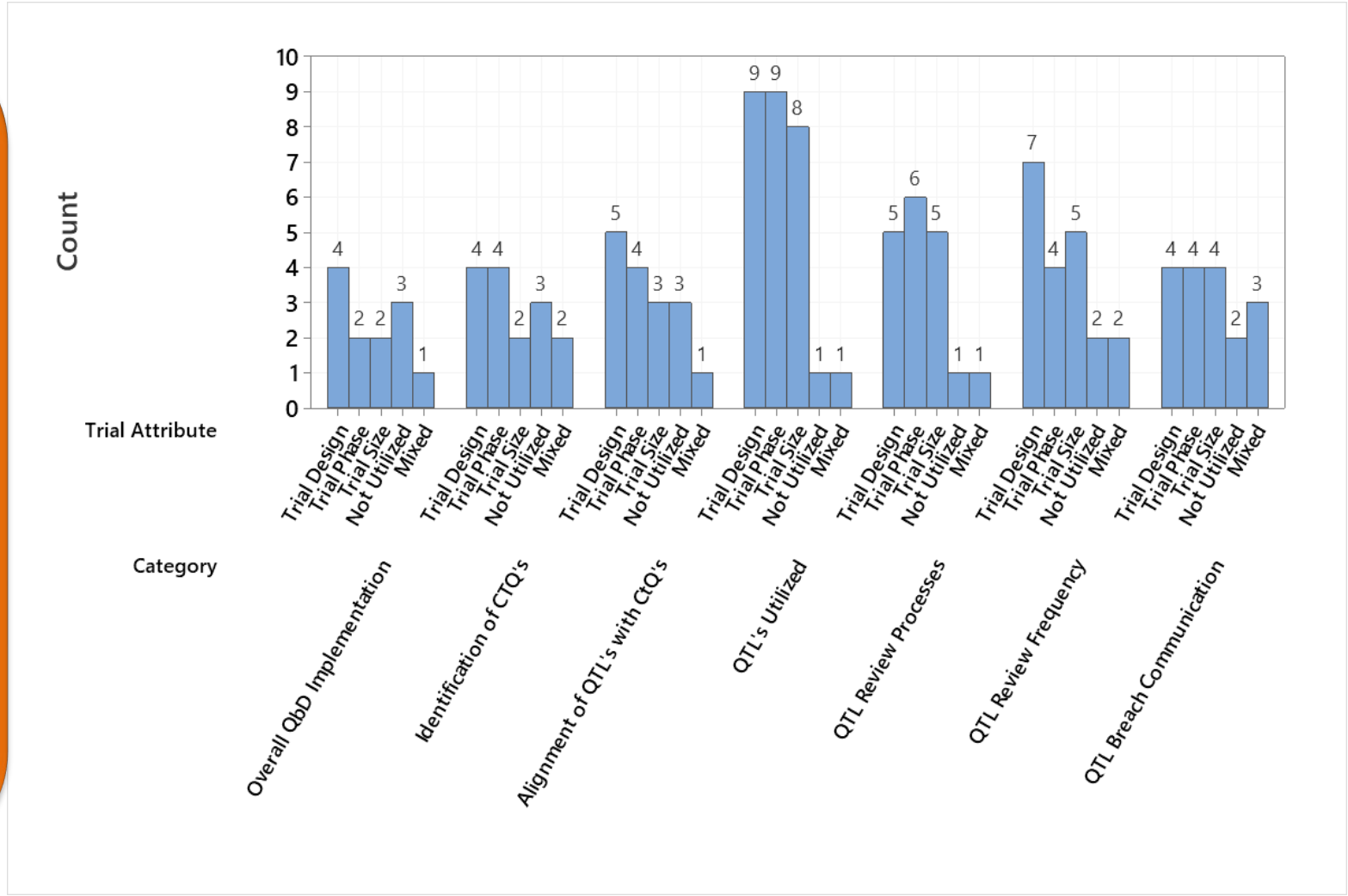
- Industry maturing
- Opportunity to broaden and deepen engagement and drive enhanced effectiveness and efficiency
- A culture of quality and learning can be achieved (**>70%** of respondents have feedback loops in place)



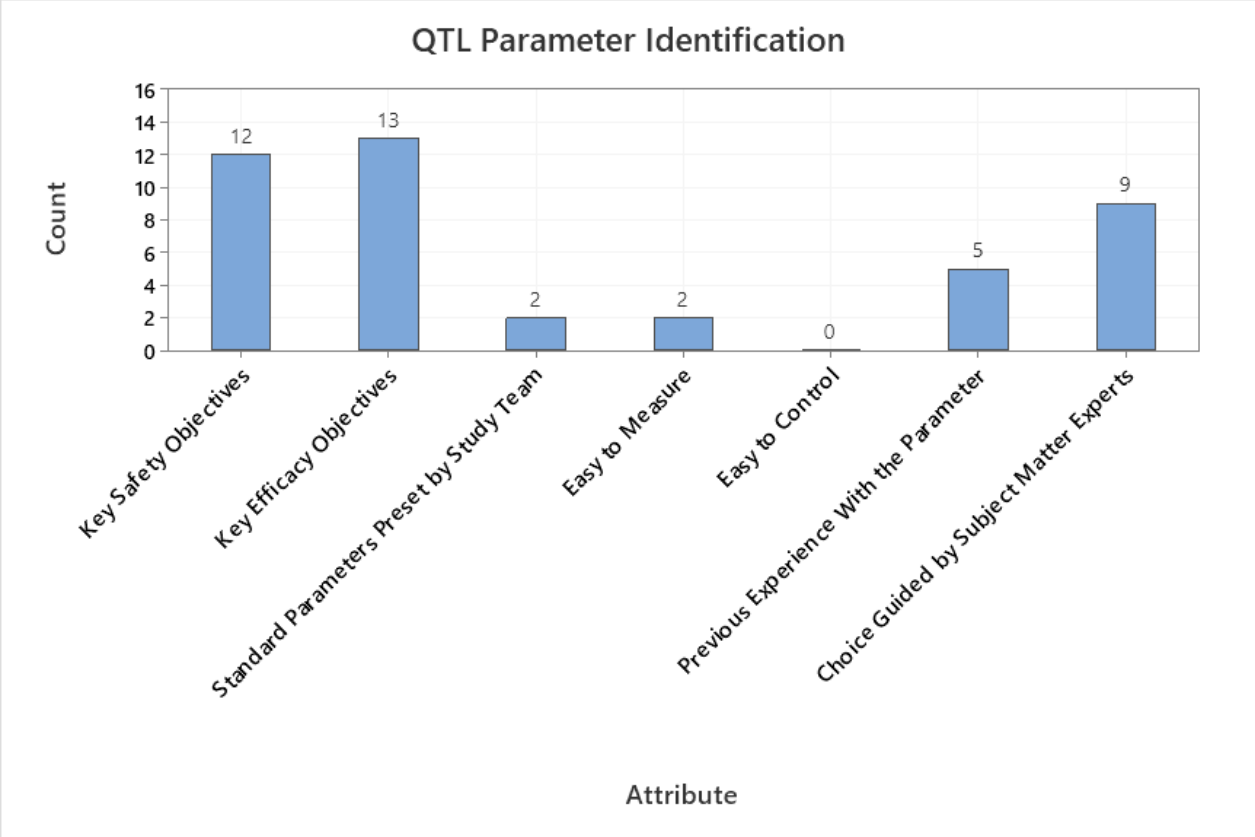
Challenges to the Application of RBQM

Trial Design, Phase and Size

- Most impactful on use of QTLs, their review processes and frequency
- Less impactful on QbD implementation, CtQ identification, QTL breach communication



Implementation of QTLs



QTL implementation focused on key clinical trial safety & efficacy objectives

Do QTL's Surface An Underlying Systemic Issue?

53%
Rarely or Never

46%
Most of the Time

Do QTL's Control the Intended Risk?

52%
Always or Most of the Time

47%
Rarely or Never

QTL Threshold Derivation

QTL Threshold team addressed actual approaches for QTL monitoring:

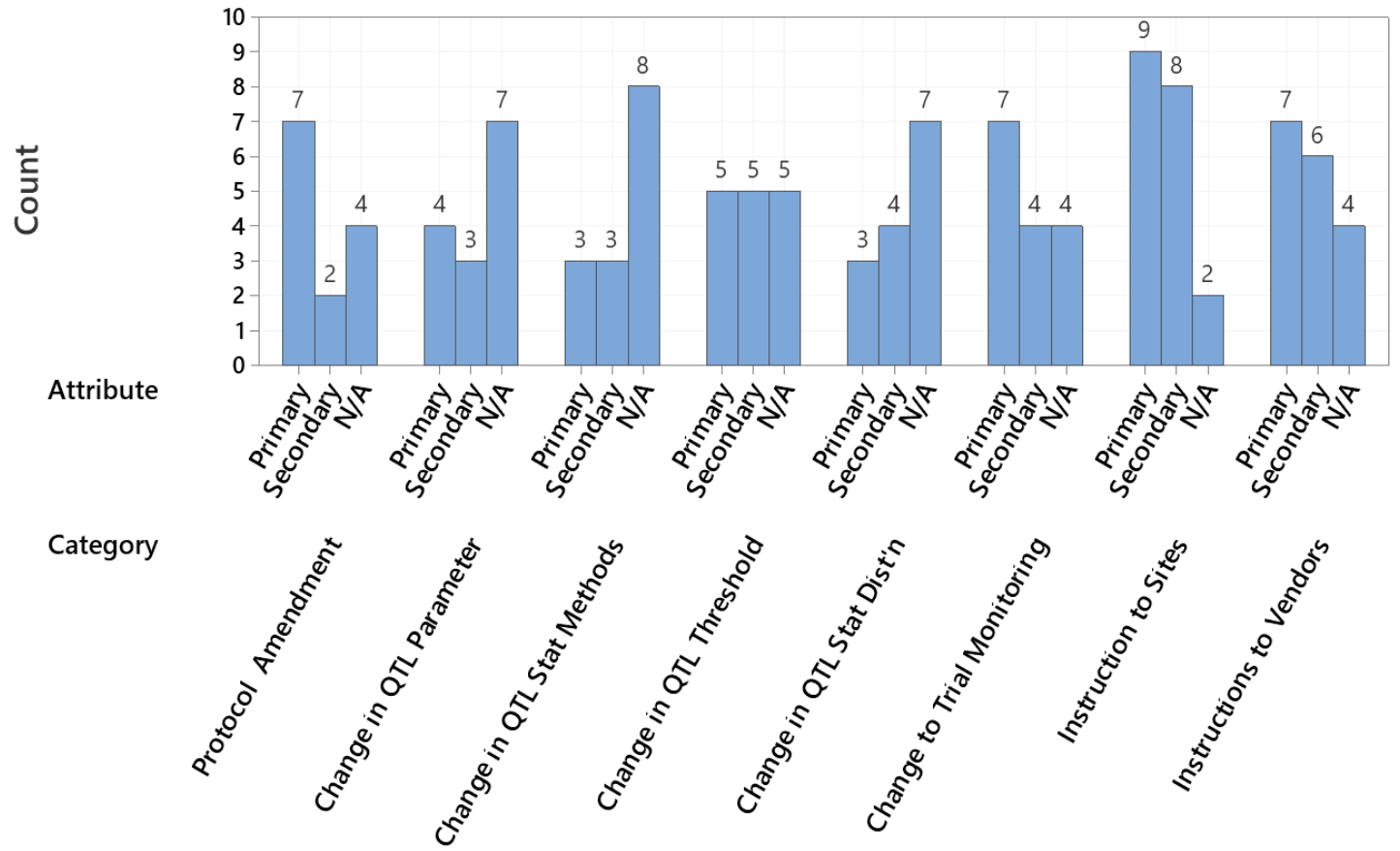
Challenges / Opportunities	QTL Monitoring Recommendations*
Alignment on ICH E6 (R2) interpretation	Clarification of terminology/definitions within QTL framework
QTL parameters primarily defined as proportions or rates Thresholds primarily defined by experts with support of statistical methodology	Proposal on statistical methodology for data driven threshold derivation for QTL monitoring Defining applicability in various situations (e.g. smaller companies)

*A.Keller, N.v.Borrendam et al., Quality Tolerance Limits: A General Guidance for Parameter Selection and Threshold Setting, submitted and accepted in Therapeutic Innovation and Regulatory Science

QTL Deviations

Oversight Methodologies

- Focus on ensuring protocol achieves desired outcomes
- Investigations to monitoring, site and vendor oversight are important breach actions
- Review of QTL parameters & thresholds may be required in some instances



Reflections

RBQM Adoption Continues to Mature

- Focus on critical data and processes that align with CtQs and QbD
  - Experience suggests there are challenges understanding Critical Data to be identified that align with the CtQs
  - Estimand Framework and Key Safety criteria can identify key trial outputs which in turn can define the required Critical Data and the relevant CtQs
- QTLs should evolve out of the CtQ discussion
- ICH E6 (R3) may pave the way

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- **QTL Thresholds Team Co-Leads**
  - Nathalie van Borrendam (Johnson & Johnson), Annett Keller (Boehringer Ingelheim)
- **RBQM Working Group Co-Lead**
  - Jeremy Howells (Roche)
- And the wider RBQM Working Group and PHUSE organization

Thank You!

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Moderated Discussion and Audience Q&A

Moderator:

Laurie Muldowney,

US Food and Drug Administration

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Our Program Will Resume 3:10 pm ET

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Session 4: Next Steps for Implementing Quality Management of Clinical Investigations

Moderator: **Ann Meeker-O'Connell,** US Food and Drug Administration

Speakers:

Danilo Branco, Fortrea

Michael Torok, Genentech

Kelsie Pearson, Cystic Fibrosis Foundation

Peter Stein, US Food and Drug Administration

Join at
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Moderated Discussion and Audience Q&A

Moderator:

Ann Meeker-O'Connell,

US Food and Drug Administration

Concluding Remarks

Marianne Hamilton Lopez

Senior Research Director, Duke-Margolis Institute for Health Policy

Thank You!

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