Achieving Fit-for-Purpose Clinical Trial Quality

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Clinical Investigator Training Course– December 12, 2024

Learning Objectives

- Discuss FDA's perspective on clinical trial quality and the meaning of fitness for purpose.
- Understand how quality-by-design and risk proportionality principles are applied in the design and conduct of clinical trials.
- Discuss implementation of risk mitigation strategies and proactive measures (at the site-level) to avoid protocol noncompliance and errors that matter.
- Provide a case example that illustrates the benefits of using QbD and risk proportionality approaches to the design and conduct of clinical trials.

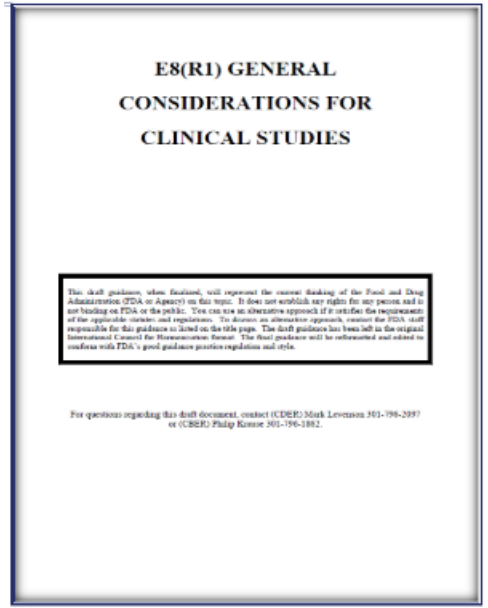
FDA Requirements: Clinical Trial Quality

- 21 CFR 314.126 broadly describes what constitutes an adequate and well-controlled study*
  - Study design permits a valid comparison with a control to provide a quantitative assessment of drug effect
  - Method of selection of subjects provides adequate assurance that they have the disease or condition being studied
  - Method of assigning patients to treatment and control groups minimizes bias and assures comparability of the groups
  - Adequate measures are taken to minimize bias
  - Methods of assessment of subjects' response are well-defined and reliable

* The primary basis for determination of whether “substantial evidence” has been provided to support the claims of effectiveness for new drugs

How Do We Define Quality?

- **ICH E8(R1)[1]:** Quality of a clinical trial is considered fitness for purpose
  - The quality and amount of the information generated in a clinical trial should be sufficient to support good decision-making
- **CTTI[2]:** Quality of a clinical trial is defined as the avoidance of errors that matter to decision making—that is, avoidance of errors that have a meaningful impact on the safety of trial participants or credibility of the results


E8(R1) GENERAL CONSIDERATIONS FOR CLINICAL STUDIES

[1]See ICH E8(R1) Final Version, Adopted on 6 October 2021 https://database.ich.org/sites/default/files/E8-R1_Guideline_Step4_2021_1006.pdf

[2]See Clinical Trials Transformation Initiative (CTTI), Quality-by-Design Projects- available at https://ctti-clinicaltrials.org/our-work/quality/quality-by-design/

Clinical Trial Quality

- Multiple parties have responsibility for trial quality and participant protection, including:
  - Sponsors
  - Contract Research Organizations (CROs) and other service providers performing clinical trial activities
  - Institutional Review Boards
  - **Clinical Investigators**

Quality by Design

- QbD entails proactively designing quality into the study to ensure:

The protection of the rights, safety, and well-being of study participants

The generation of reliable and meaningful results

The **management** of risks to critical study factors using a risk proportionate approach

ICH E8(R1) Step 4: https://database.ich.org/sites/default/files/E8-R1_Guideline_Step4_2021_1006.pdf

Why at the Design of Trial?

Purpose of a Clinical Trial

- To generate reliable information to answer research questions and to support decision-making
- To support the development of new medicines or uses of existing medicines

Well Designed and Conducted Trials

- Help answer key questions in health care and drug development
- Are relied upon by many in health care and drug development and their results are essential for evidence-based healthcare decisions

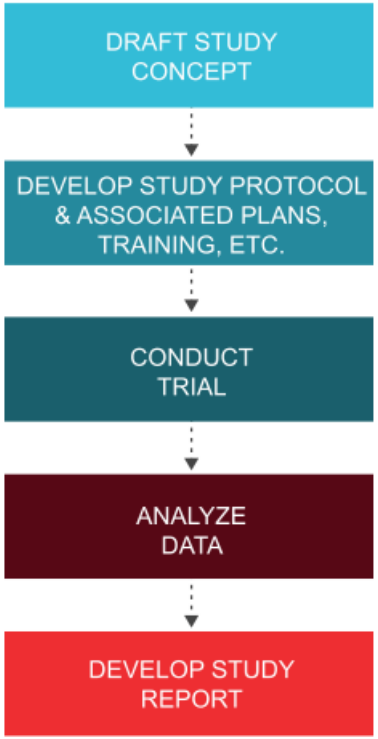
Poorly Designed and Conducted Trials

- Place participant safety at risk, yield unreliable and/or inadequate evidence, waste resources, and may not align with ethical principles

The Risk of Not Building Quality Into the Study Foundation

- We don't want to see a fire fighting mentality applied to clinical trials where the sponsor/CRO/CIs are frantically rushing, making impulsive decisions; applying "Band-Aids" to problems without in-depth investigation, suppressing problems with short-term solutions
- This could result in
  - Loss of data integrity and in the rejection of the study to support regulatory and therapeutic decisions
  - Discontinued development of potentially beneficial therapy

Protocol Development: A Crucial Component of Quality by Design



1. Identify critical aspects of trial design
2. Tailor design to avoid errors that matter
3. Streamline trial where feasible
4. Verify proposed design is consistent with important scientific question to be addressed
5. Highlight important risks not eliminated through study design that may be better addressed in operational plans

https://ctti-clinicaltrials.org/our-work/quality/quality-by-design/

fda.gov/cdersbia

Focus on What Matters: Critical-to-Quality Factors

- Critical-to-quality (CTQ) factors: attributes of a study whose integrity is fundamental to the
  - Protection of study participants
  - Reliability and interpretability of the study results
  - Decisions made based on the study results
- Why are they considered CTQ?
  - If their integrity were to be undermined by errors of design or conduct, the reliability or ethics of decision-making based on the results of the study would also be undermined

CTQ Factors

- Are identified and reviewed at the time of design and planning of the trial
- Are re-reviewed and re-assessed throughout the trial conduct, analysis, and reporting
- Are individualized per the study design (i.e., one size fits all approaches should be avoided)
- Should be communicated to all those involved in trial conduct to ensure a shared understanding and alignment on what is CTQ and the quality expectations

Challenge Question #1

Which of the following best defines the concept of QbD in clinical trials?

A. A reactive approach to quality control that addresses issues after they occur.

B. A proactive approach that emphasizes designing quality into the trial from the outset.

C. A method focused solely on data collection and statistical analysis.

D. An approach that prioritizes regulatory compliance over participant safety.

Challenge Question #2

In implementing QbD, which of the following elements is MOST critical for ensuring clinical trial quality?

A. Randomization of participants

B. Comprehensive understanding of the study's CTQ factors and potential risks to those CTQ factors

C. Strict adherence to standard operating procedures

D. Extensive documentation of all trial activities

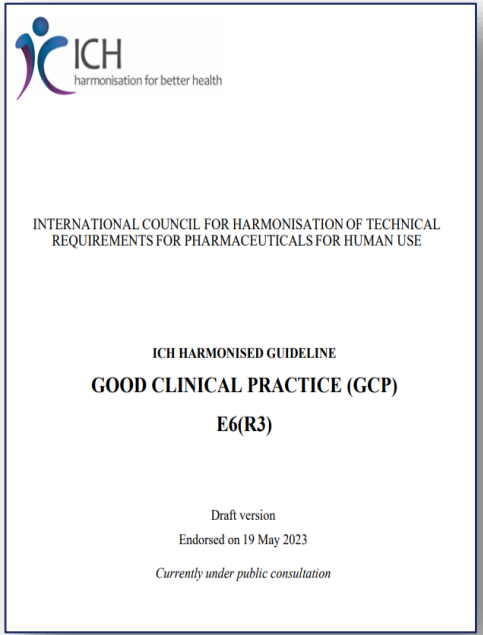
ICH E6 (R3): Annex 1 and Annex 2

Annex 1: Considerations for interventional clinical trials

- Provides recommendations on how the principles can be appropriately applied to clinical trials

Annex 2: Additional considerations for interventional clinical trials

- Provides recommendations on the appropriate application of the principles in clinical trials that incorporate various operational approaches and data sources (e.g., decentralized elements, pragmatic elements, and/or RWD sources)


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

Source: https://database.ich.org/sites/default/files/ICH_E6%28R3%29_DraftGuideline_2023_0519.pdf

ICH E6 (R3): Purpose of the Update

To provide recommendations that:

- Are applicable to a broad range of clinical trial designs
- Facilitate modernization, harmonization and innovation in trial design, technology, and data sources
- Address the complexities of clinical trials in the current global regulatory climate

To further advance:

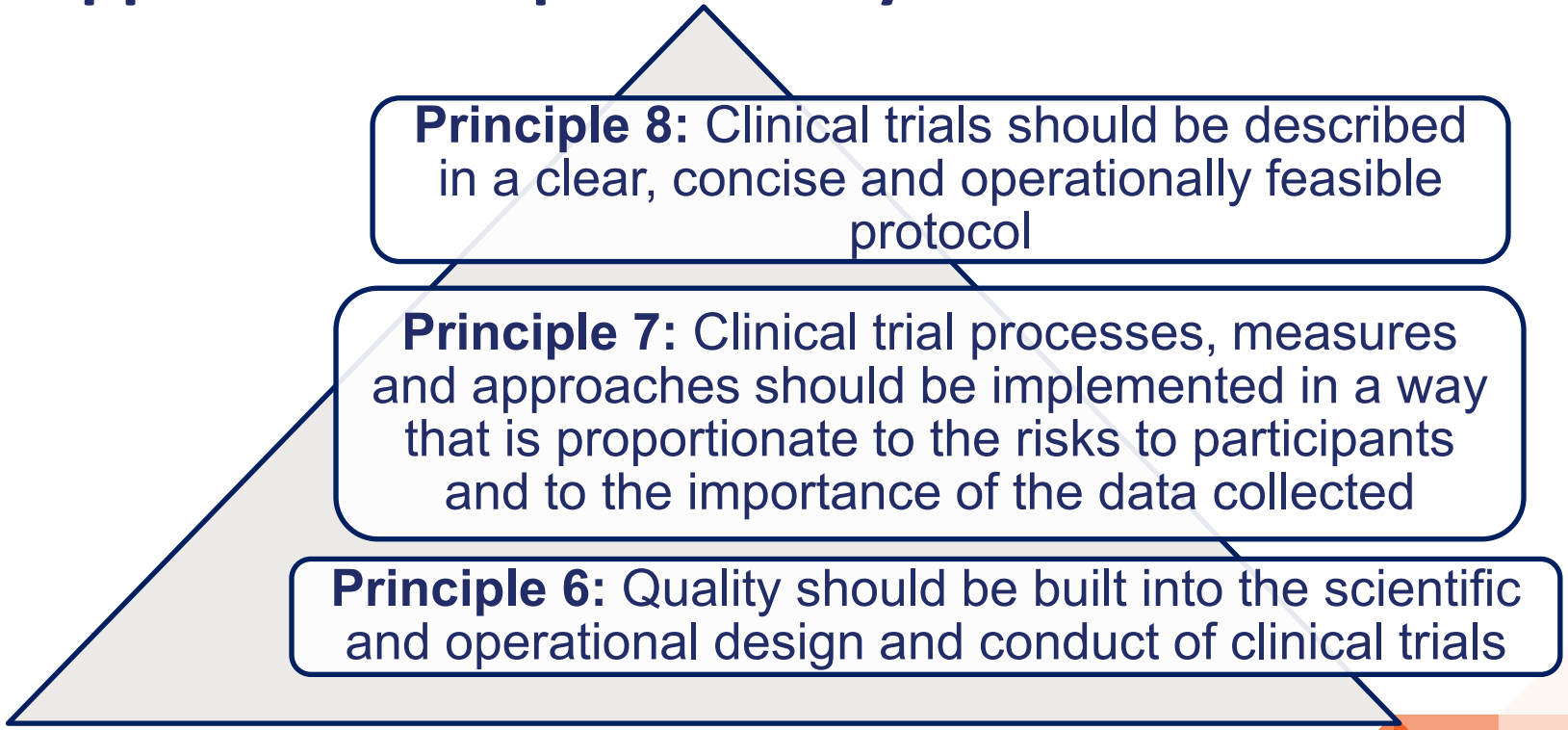
- The design and implementation of efficient clinical trial protocols and tools and procedures for trial conduct through adoption of QbD
- Risk-proportionality and fit- for-purpose clinical trial quality

To provide flexibilities:

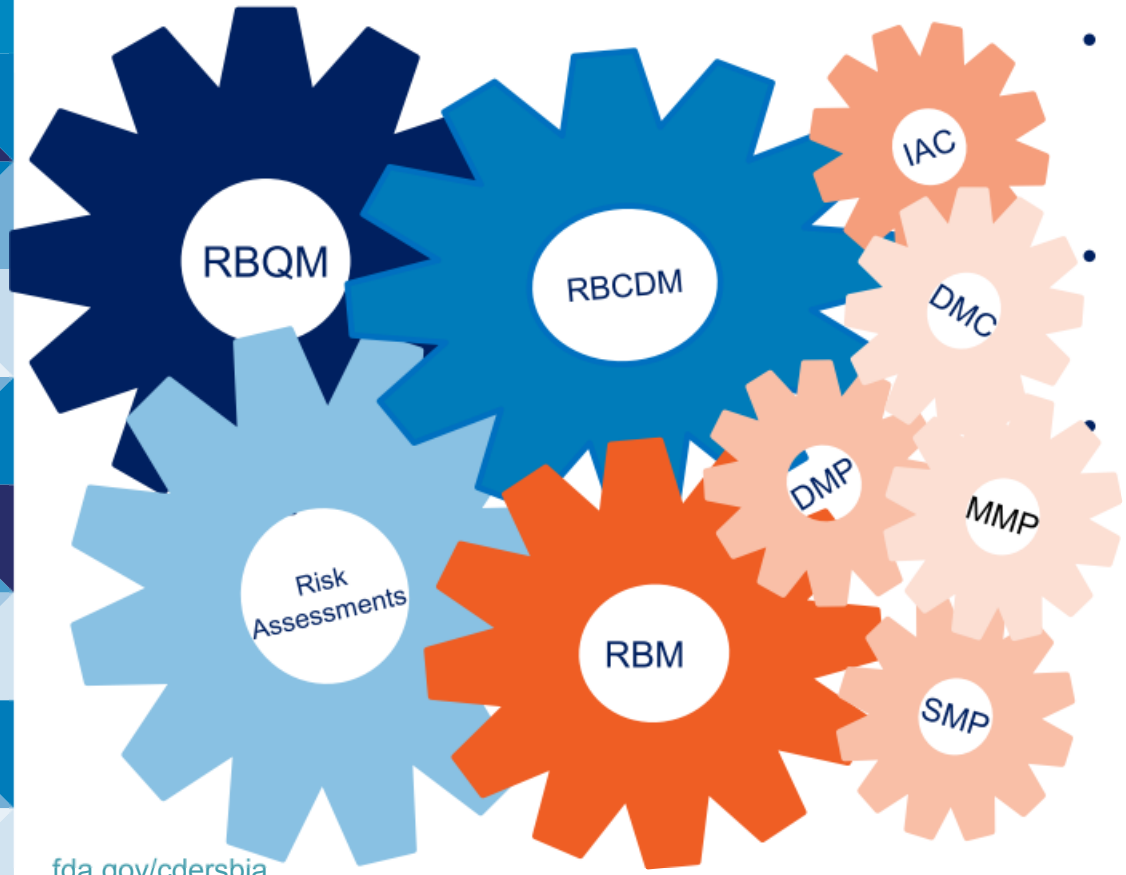
- When applying the principles and guideline such that they are fit for purpose for the design and conduct of the clinical trial

Source: https://database.ich.org/sites/default/files/ICH_E6%28R3%29_DraftGuideline_2023_0519.pdf

ICH E6 (R3): Key Foundational Principles That Support Risk Proportionality



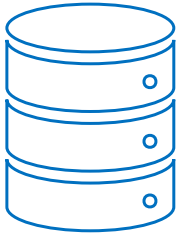
Risk Proportionality Expectations



- Study plans and processes should all feed from your QbD approach
- Risk assessments and management processes are iterative
- Errors that involve critical trial data or subject safety should be identified and corrected as early as possible or avoided all together

Risk Proportionality Expectations For Clinical Investigators

- Ensure a comprehensive and shared understanding of the study's CTQ factors and potential risks to those CTQ factors
- Focus resources and investigator oversight on critical data points and high-risk areas (i.e., data and processes deemed CTQ)
- Assess risks throughout the study, adapting practices as necessary to respond to new information or unforeseen challenges that may arise in study conduct



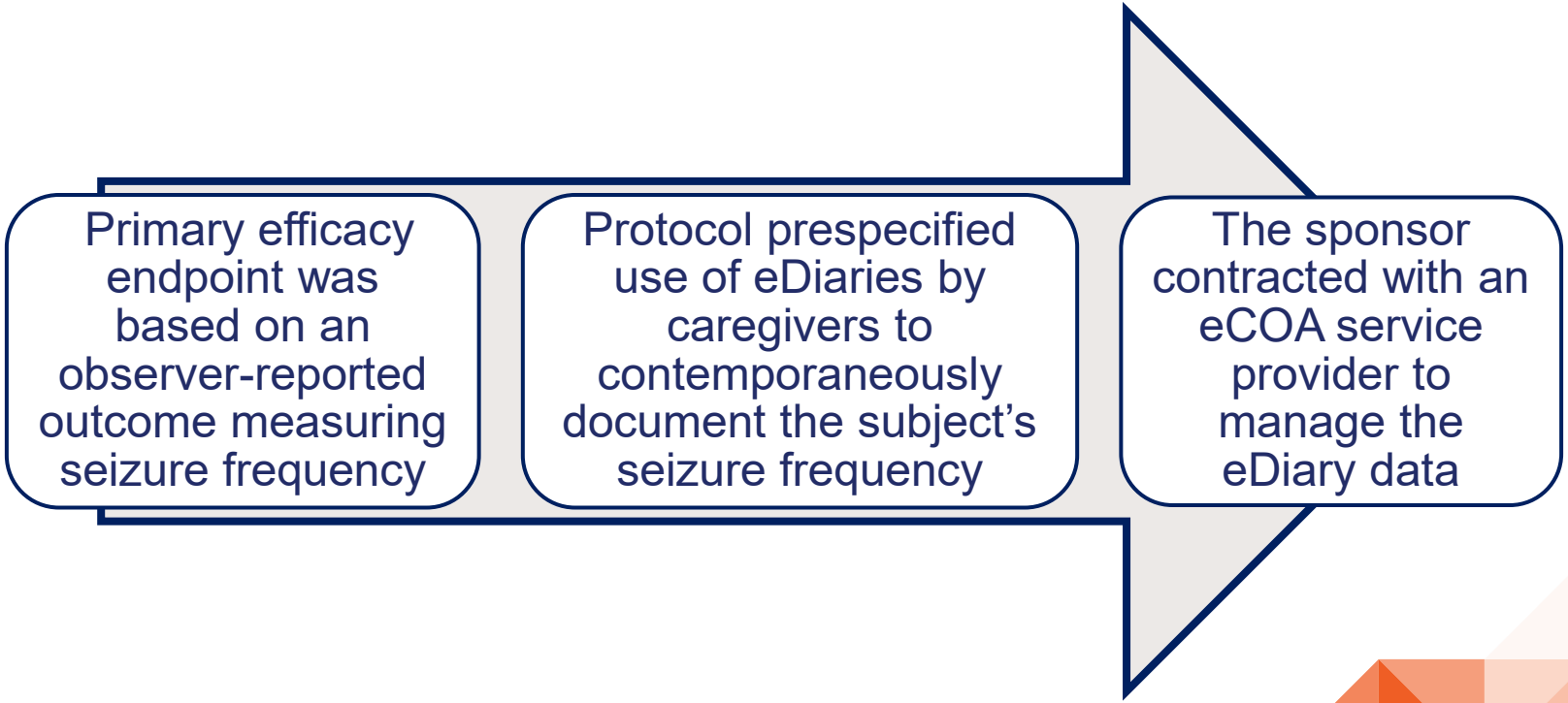
Case Example on the Use of Electronic Diaries (eDiaries) in a Clinical Trial

Background

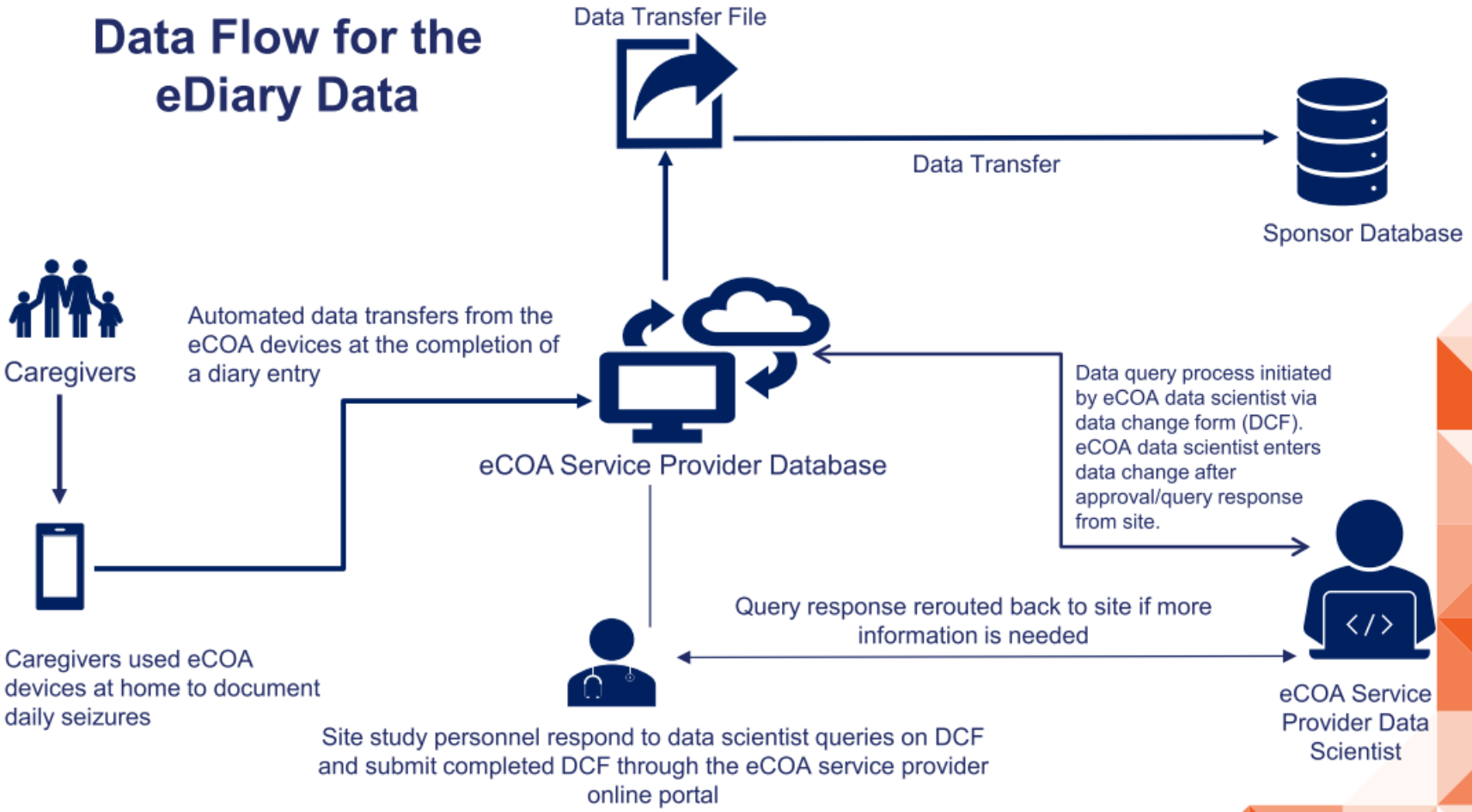
Two pivotal trials: multicenter, randomized, double-blind, placebo-controlled studies that compared the efficacy and safety of an investigational drug to placebo as adjunctive therapy in patients with a seizure disorder

The ***primary efficacy endpoint --*** was the change in the mean convulsive seizure frequency during the Treatment Period compared with the Baseline Period

Case Example: Use of eDiaries



Data Flow for the eDiary Data



Inspection Observations

A review of the eCOA system audit trails revealed that a substantial portion of eDiary data was collected retrospectively

Retrospective data collection took place up to one year after the original date when the data should have been collected

What Happened?

- More than the expected amount of missing data
- CIs retrospectively collected the missing eDiary data to salvage the amount of missing primary efficacy endpoint data
- CIs and study staff retrospectively collected data by
  - Conducting in-person and phone interviews with caregivers
  - Collecting and reviewing caregivers' personal diaries and notes
- Caregivers' personal diaries were not designed for use in the trial and did not collect all of the protocol-required information (e.g., time and type of seizures, dosing, and use of rescue medications)

Inspection Observations

Source records, such as caregivers' personal diaries, required to verify the retrospectively collected eDiary data were not consistently maintained or retained at the sites

Multiple discrepancies were identified between the available source records for the retrospectively collected diary data and the sponsor’s data listings

The service provider staff misinterpreted data change forms and source records, such as consolidating multiple seizure events into a single seizure event

Root Cause of Missing Data

eDiary device design, malfunction, connectivity, and transmission issues experienced during the conduct of the trial were not adequately and promptly addressed by the eCOA service provider and the sponsor

Poor caregiver compliance of eDiaries for various reasons

Lack of contingency plans for device malfunctions and connectivity and transmissions issues

Data Reliability Assessment and Its Implications

Clinical investigators retrospectively collected a portion of the seizure frequency eDiary data for 96% of the randomized subjects in the two studies

This affected approximately 20% the total seizure frequency eDiary data for the two studies

Because of the potential for recall bias and the inspectional observations, the retrospectively collected seizure frequency data impacted the accuracy and reliability of the efficacy results of the two studies

A post hoc sensitivity analysis was performed by both the applicant and the FDA on the primary efficacy endpoint concerning the retrospectively collected eDiary data

Lessons Learned

- Conduct risk assessments at the study's outset to identify CTQ factors and risks to CTQ factors
- Prioritize resources and implement targeted strategies for high-risk areas to maintain data quality
- Adjust oversight based on assessed risks (e.g., more frequent review for high-risk components)
- Communicate quality expectations to ensure shared understanding among all team members
- Foster open communication about potential issues for quick responses and adjustments to data collection practices

Bonus: Challenge Question #3

How should the principle of risk proportionality influence the allocation of resources and the implementation of risk management strategies?

A. All processes should be standardized regardless of the level of risk involved.

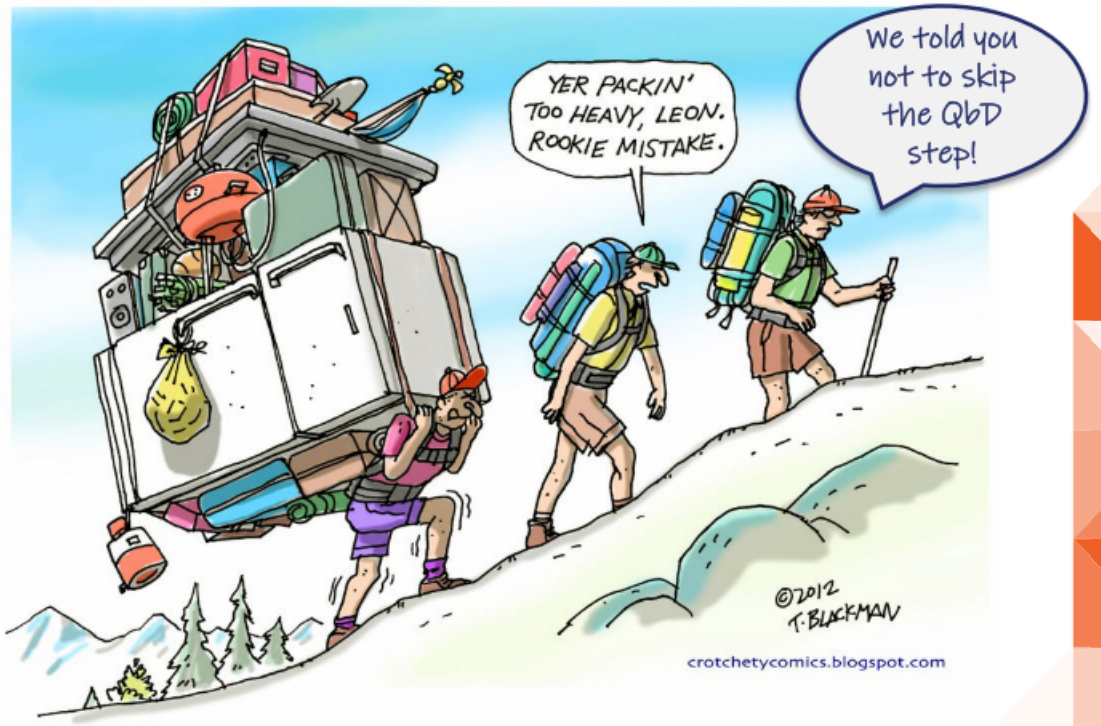
B. Risk management strategies should be minimal, as extensive measures may hinder the trial's progress.

C. Resources should be concentrated on high-risk areas and critical data points, with appropriate risk assessments guiding decisions on acceptable levels of risk.

D. The importance of data should be assessed only after the trial is completed, based on outcomes.

Closing Thought

Achieving fit-for-purpose data quality largely hinges on the foundational principles of QbD and focusing on what matters to participant safety and the reliability of the overall study results



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Questions?

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