CRITICAL PATH INSTITUTE

PRO CONSORTIUM

eCOA CONSORTIUM

A NETWORK POWERED BY PEERS

eClinical forum

Best Practice Recommendations for Electronic Clinical Outcome Assessment Data Changes

February 6, 2024

Based on the consensus paper published on December 14, 2023, in the *Journal of the Society for Clinical Data Management*

Moderator/Presenters

- **Moderator:** Scottie Kern, Critical Path Institute's eCOA Consortium
- **Presenters:**
  - Trish Shepherd Delong, J&J Innovative Medicine
  - Demian Humler, Clario
  - Alan Yeomans, Viedoc

Disclaimer

- The views and opinions expressed in the following slides are those of the individual presenters and should not be attributed to their respective organizations/companies, eClinical Forum, or Critical Path Institute.

-

Funding Acknowledgments

- Critical Path Institute is supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) and is 54% funded by the FDA/HHS, totaling $19,436,549, and 46% funded by non-government source(s), totaling $16,373,368. The contents are those of the authors and do not necessarily represent the official views of, nor an endorsement by, FDA/HHS or the U.S. Government.
  - Support for the eCOA Consortium comes from membership fees paid by members of the ePRO Consortium (https://c-path.org/programs/ecoa/).
  - Support for the Patient-Reported Outcome (PRO) Consortium comes from membership fees paid by members of the PRO Consortium (https://c-path.org/programs/proc/).
- Support for eClinical Forum comes from membership fees paid by members of eClinical Forum (https://eclinicalforum.org/).

Agenda

- Background
- Objective
- Challenges
- Recommendations
- Questions/Discussion

About the PRO Consortium and eCOA Consortium

Patient-Reported Outcome (PRO) Consortium:

- The PRO Consortium was formed in late 2008 by C-Path in cooperation with FDA's Center for Drug Evaluation and Research and the pharmaceutical industry. Its mission is to establish and maintain a collaborative framework with appropriate stakeholders for the qualification of PRO measures and other clinical outcome assessments (COAs) that will be publicly available for use in clinical trials where COA-based endpoints are used to support product labeling claims.
- For further information, visit https://c-path.org/programs/proc/

Electronic Clinical Outcome Assessment (eCOA) Consortium:

- The eCOA Consortium was established by C-Path in 2011. Along with C-Path, its members are firms that provide electronic data collection technologies and services for capturing PRO and other COA data electronically in clinical trials. Its mission is to advance the science of clinical trial endpoint assessment by collaboratively supporting and conducting research, designing and delivering educational opportunities, and developing and disseminating best practice recommendations for electronic collection of clinical outcome data.
- For further information, visit https://c-path.org/programs/ecoac/

About the eClinical Forum

The eClinical Forum (eCF) is a global, technology independent group representing members of industries engaged in clinical research. The eClinical Forum's mission is to serve these industries by focusing on those systems, processes and roles relevant to electronic capture, handling, and submission of clinical trial data. The eClinical Forum has sought out opportunities to promote electronic Clinical Trials since its inception in 2000. The cross-industry forum has a broad view of research with members - Sponsors, Contract Research Organizations (CROs), Technology vendors (both clinical research and healthcare), Academia, and Investigators - and with invited outreach opportunities with global Regulatory representatives.

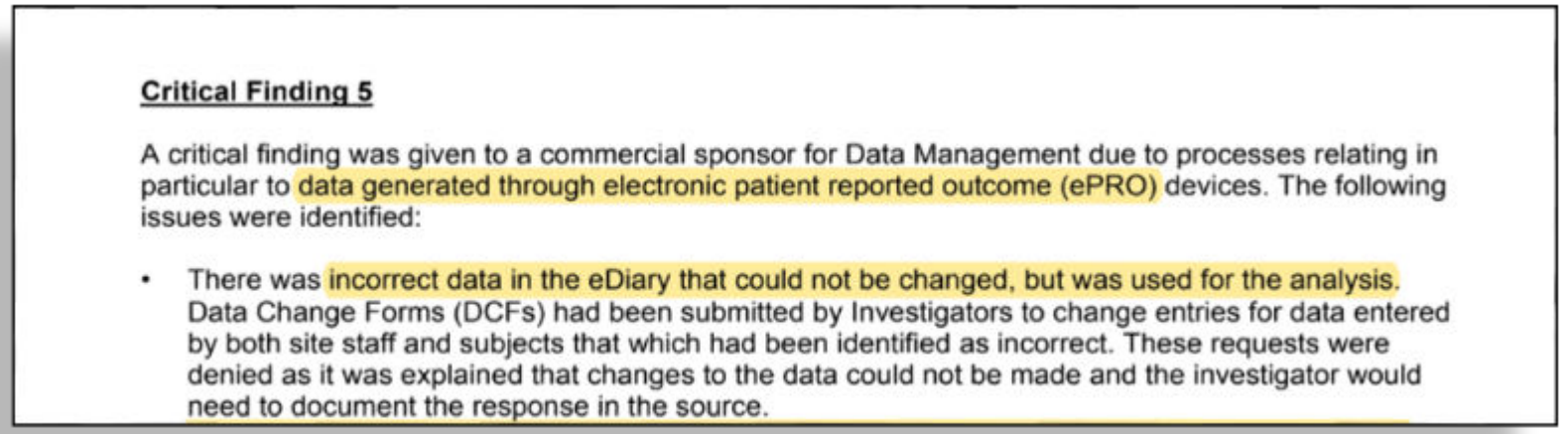
For further information visit the website at www.eclinicalforum.org.

Background

Some providers were implementing data change rules (developed by the eCOA providers and/or sponsors) that stated which data were permitted and not permitted to be changed that involved, in most circumstances, approval by the sponsor.

Historic approaches to eCOA data changes:

- "No changes will be allowed to patient-entered data."
- "Changes to endpoint data require sponsor pre-approval."



Critical Finding 5

A critical finding was given to a commercial sponsor for Data Management due to processes relating in particular to data generated through electronic patient reported outcome (ePRO) devices. The following issues were identified:

- There was incorrect data in the eDiary that could not be changed, but was used for the analysis. Data Change Forms (DCFs) had been submitted by Investigators to change entries for data entered by both site staff and subjects that which had been identified as incorrect. These requests were denied as it was explained that changes to the data could not be made and the investigator would need to document the response in the source.

MHRA Critical Findings (GCP Inspections 2016-2017)

"There was a loss of PI control of data between database lock and pdfs being sent to the site. The pdfs returned were also only the final version of the data and did not contain all meta data."

Project Objective

To bring together experts across the eCOA industry to develop best practice recommendations for industry on handling patient-reported data change requests.

Challenges

Despite Numerous Regulatory References, Ambiguity Existed

Record keeping and retention: "An investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual..." *(FDA 21CFR312.62 (b))*

Corrections of eSource: "A procedure should be in place to address the situation when a study subject or other operator capturing data, realises that he/she has made a mistake and wants to correct the recorded data." *(EMA reflection paper 2010)*

Responsibilities of Sponsors: "Sponsors are responsible for selecting qualified investigators, providing them with the information they need to conduct an investigation properly, ensuring proper monitoring of the investigation(s), ensuring that the investigation(s) is conducted in accordance with the general investigational plan and protocols contained in the IND..." *(FDA 21CFR312.50)*

Control of eSource:
"Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e., an audit trail should be maintained)… Sponsors should provide guidance to investigators and/or the investigators' designated representatives on making such corrections." *(ICH GCP 4.9.3)*

EMA Guideline on Computerised Systems 2023

The protocol should identify any data to be recorded directly into the eCRFs and considered to be source data (ICH-GCP 6.4.9). ***This is equally applicable to other specific data collection systems, such as ePRO****. Data directly captured in these tools without prior identification in the protocol to be source data is considered as GCP-noncompliant.**

- *A procedure should be in place to address the situation when a data originator (e.g. investigator or trial participant) realises* ***that she/he has submitted incorrect data by mistake and wants to correct the recorded data*****.**
- *Data changes for ePRO typically differ from that of other EDC tools because trial participants may not have access to correct data in the application.* ***Hence, procedures need to be in place in order to implement changes when needed.*** *This depends on the design of tools and processes and could be in the form of data clarification processes initiated by trial participants on their own reported data or initiated by investigators.*
- *Data reported should always be reliable.* ***Data clarification procedures*** *introduced by the sponsor or service provider, whether or not described in the protocol* ***should not prohibit changes in trial participant data when justified*** *e.g. if the trial participant realises that the data have not been entered correctly*.

* Guideline on computerised systems and electronic data in clinical trials
EMA/INS/GCP/112288/2023

EMA Guideline on Computerised Systems 2023

- *It is expected that the possibility for changes is implemented based on a **justified and trial-specific risk-assessment and that any changes are initiated in a timely manner by the participant or site staff** and in case of the latter is based on solid source at investigator sites e.g. phone notes or emails from trial participants documenting the communication between sites and trial participants immediately after the error was made/discovered.*

- *One of the advantages of direct data entry by the trial participant is that recall bias is minimised as the data are entered contemporaneously. **Consequently, corrections should not be done at a much later stage without good reason and justification.** Whether collected by paper or electronic means, the regulatory requirements are that all clinical data should be accurately reported and should be verifiable in relation to clinical trials.*

- ***It is expected that the number of changes to ePRO data are limited**; however, this requires both designs of ePROs that are appropriate to ensure proper understanding by trial participants and appropriate training of trial participants, thereby avoiding entry errors."**

* Guideline on computerised systems and electronic data in clinical trials
EMA/INS/GCP/112288/2023

Summary of Challenges

Issues identified in regulatory inspections:

- Questions around sponsors having exclusive control of a site's data
- Changes that were made without the acknowledgment of the site
- Loopholes and process that would enable sponsors to exert control over site data

Challenge of applying regulations in a uniform way:

- Procedures developed by a variety of bodies for application in a range of different settings
- Regulations do not provide uniform guidance on the appropriateness of data modifications to PRO data

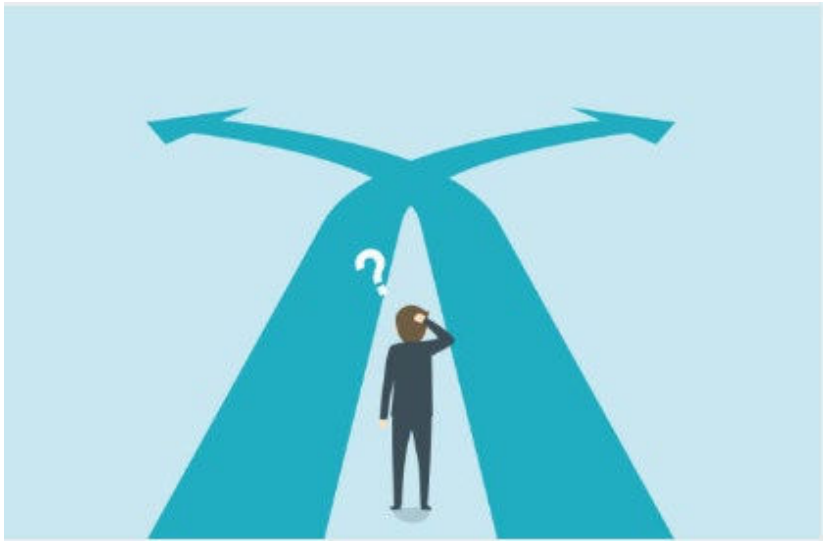
Varying implications of changing the data:

- Not all data changes have the same impact
- Revisions to certain data points may impact critical study outcomes (e.g., study eligibility or key endpoint(s))

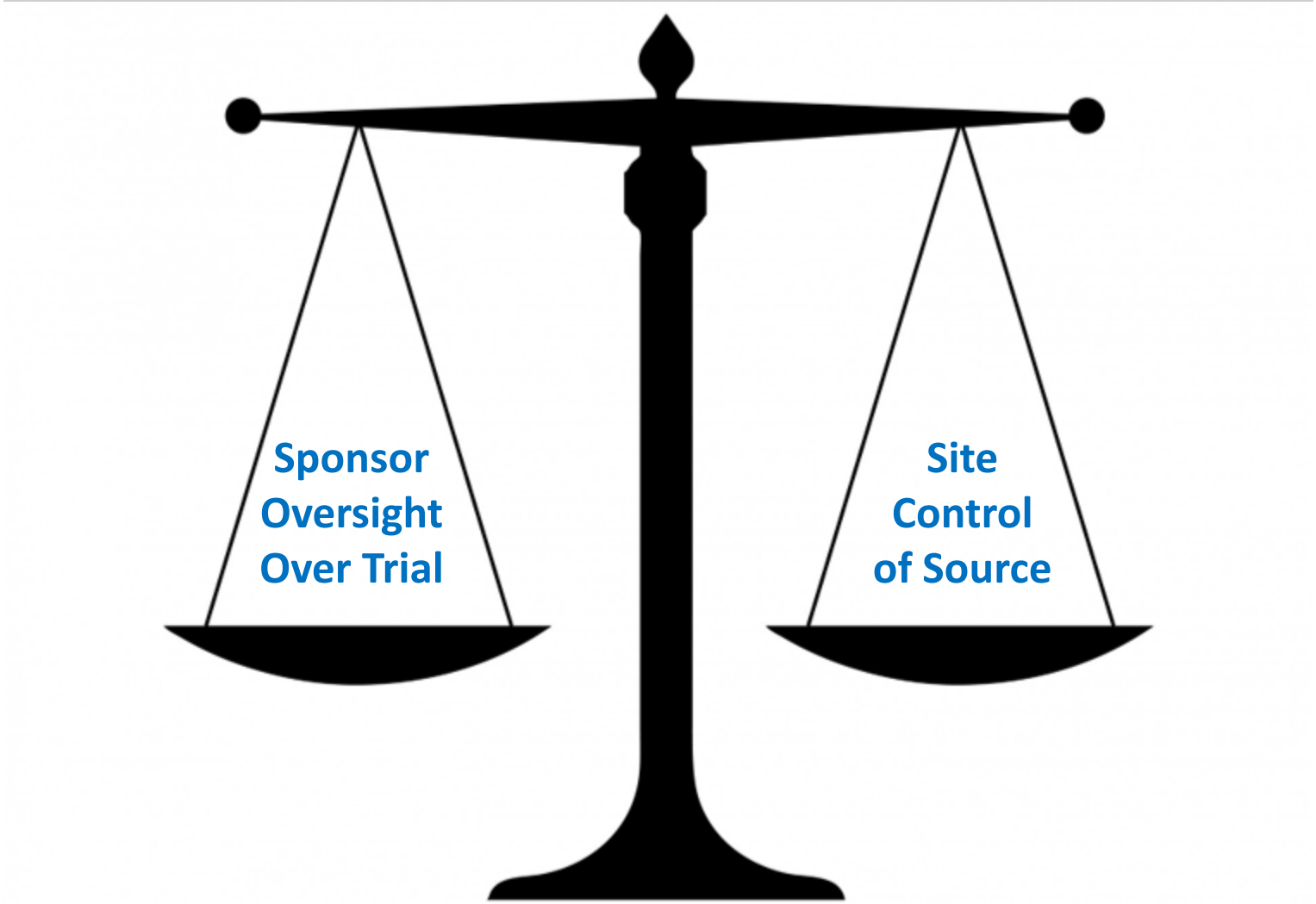
Scenario

- A patient notifies a site they want to change their answer because they made a mistake.
- Example: The patient got the ends of the scale (1-10) confused. The patient selected “3” instead of “7” and would like to change their response.

What do we do?



The Balance of eCOA Data Collection



Recommendations

Stakeholder Collaboration: Concepts

Seven Core Principles (1-4)

1. In accordance with the definition of patient-reported outcome data, clinical data values should **always reflect the respondent's chosen response** without bias or interpretation by a third party.

2. The clinical data value should be recorded in a manner consistent with the user guide and administration instructions of the assessment, including the recall period, if specified. Data changes **should not be permitted if the revised value could be subject to sources of bias** that could call into question the validity and integrity of the data.

3. **Source data changes should not compromise compliance** with Attributable, Legible, Contemporaneous, Original, Accurate, Complete, Consistent, Enduring and Available (**ALCOA+**) principles.

4. All data changes should be fully recorded in the **system(s) audit trail to enable the site to have access** to complete the eSource record and to **allow the sponsor to determine** and document the entries to be included in the statistical analysis.

Seven Core Principles (5-7)

5

Sponsors are responsible for the oversight of the service provider, including the development of an oversight plan (e.g., Data Management Plan) to define the following:

- **Identification of critical data points**, as well as non-critical/procedural data points.
- **Expectations for the investigative site** around the DCR process and documentation requirements.
- The process on when and how to **notify the sponsor** (and/or CRO), at the appropriate time, such as upon receipt of the DCR.
- **Sponsors have the responsibilities** to train sites, and to monitor, evaluate and provide guidance on DCRs that **could impact the trial**

6

Sites are expected to submit DCRs related to clinical when discrepancies are found, if sponsor (or delegate) users submit DCRs on behalf of the sites, site authorization for each request is required. Changes to system data or meta-data should be handled independently of this workflow.

7

eSource data change requests should **be supported by documentation to reconstruct the eCOA data events**, including the site personnel who requested and approved the change, date and time of change, and justification for change request as agreed upon by the data originator at the time the change was requested.

The Oversight Plan

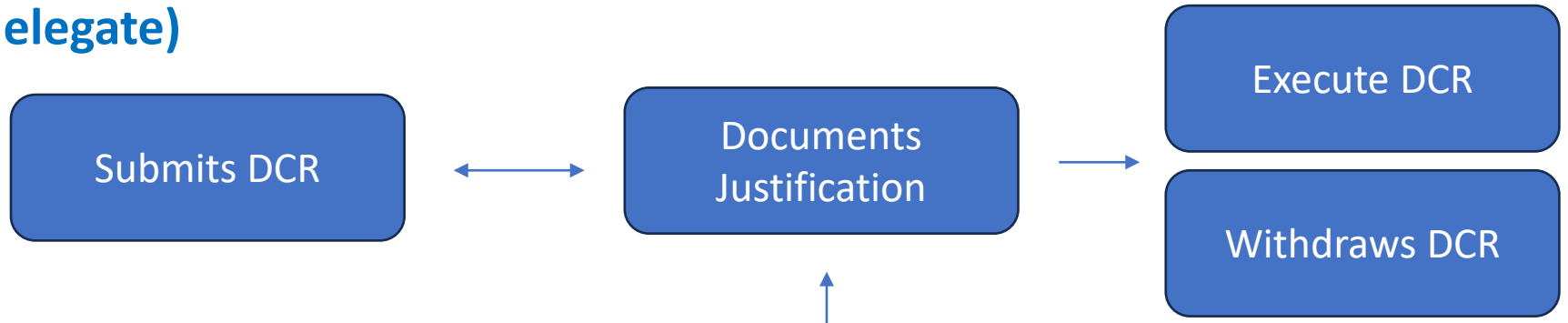
The **Oversight Plan** defines the process and technical details related to each type of change. It also defines which DCR types are **critical** or **non-critical/procedural**.

Critical Data Points are defined at the trial level in the documentation provided to the eCOA provider prior to the start of the trial. The following characteristics can deem data as critical for eSource DCRs:

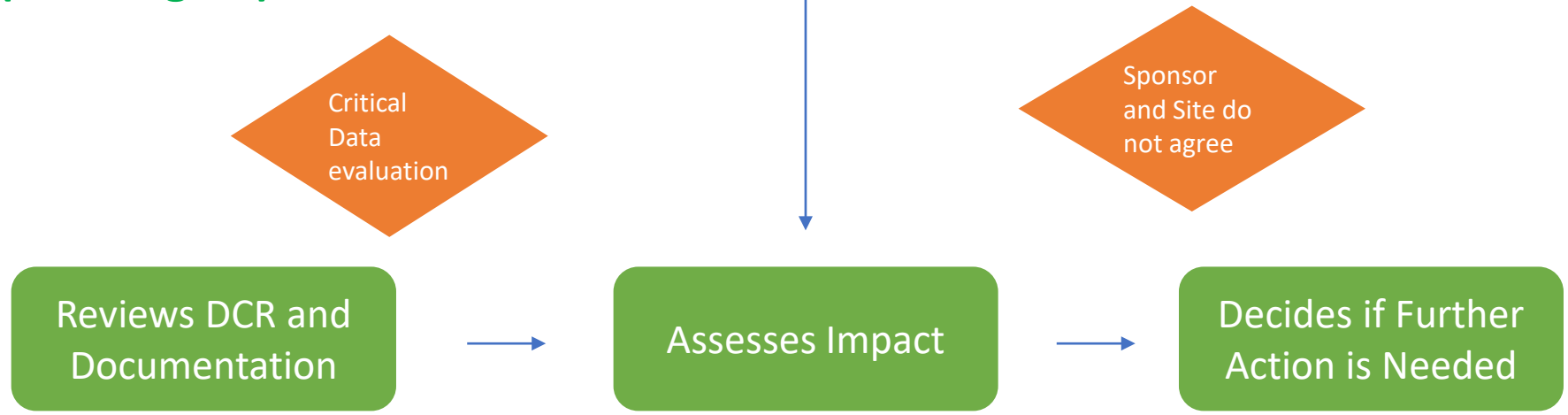
1. Data changes that may affect participant safety
2. Patient- or caregiver-entered data
3. Primary or secondary trial objectives
4. Data points that affect calculations
5. Changes to date or timestamps
6. Branching functionality

Division of Responsibility

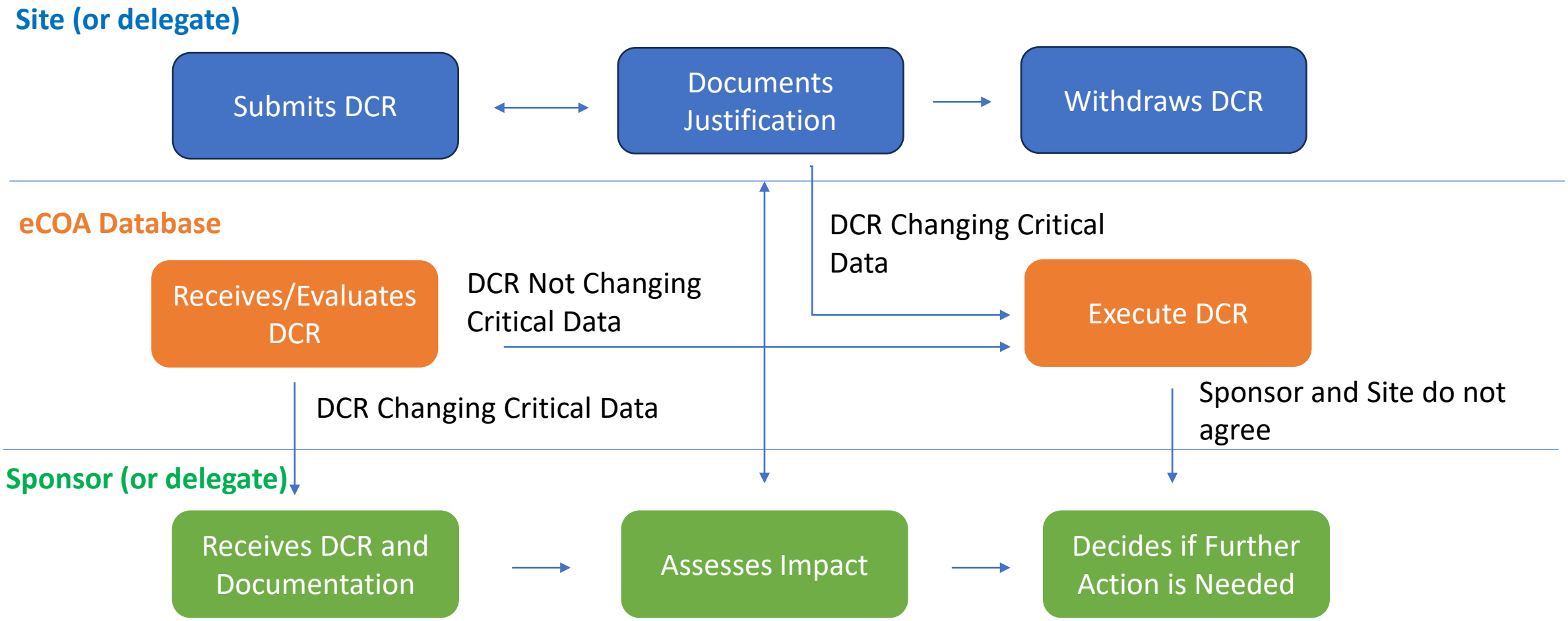
Site (or delegate)



Sponsor (or delegate)



Proactively Working Together…



Roles and Responsibilities

Site

- Maintains accurate source data
- Owns requests to change data
- Gathers supporting evidence to document the rationale of the DCR

Service Provider/ eCOA Platform

- Maintains and follows Oversight Plan
- Confirms with sites that documentation is in place for all changes to critical data
- Ensures sponsor is informed and aware of specific cases and general trends as agreed upon

Sponsor

- Ensures that sites are trained:
  - eCOA solutions
  - Expectations around DCRs
- Conducts investigations/reviews as needed around special situations pertaining to DCRs
- Performs site re-training, where necessary
- Gathers supporting evidence to document the rationale of the DCR

Risk Mitigation

Risks

1. Each eCOA service provider will use different tools and technology
   - The Oversight Plan is technology-agnostic
   - Responsibilities will vary based on platform
2. Unique scenarios not covered in the Oversight Plan
3. Derived or calculated variables may be impacted
4. Eligibility (inclusion/exclusion criteria) changes may result from requests to change patient-entered data
5. Some scenarios may involve several different errors related to critical data

Mitigations

1. Each service provider can leverage their platform to ensure
   - Sites are able to confirm documentation in place
   - Sponsors can monitor DCR trends
2. New scenarios can be added to the Oversight Plan over time
3. Special instructions for derived variables can be added to the Oversight Plan, where applicable
4. Special instructions for inclusion/exclusion can be added to the Oversight Plan, where applicable
5. Ensure regular discussions occur between service provider and sponsor, especially for unusually complex scenarios

Site and Sponsor Fail to Agree

If a sponsor disagrees with a site-initiated data change request, based on current regulations, they cannot prohibit the change.

Mitigations:

- Sponsors can and should discuss their concerns with the investigative site.
- If the site decides to reverse or withdraw the request, it is at the discretion of the site.
- If the change is implemented, the sponsor can decide whether the modified data should be excluded from the final analysis either by flagging the data in the data transfer, if possible, or by documenting the concern in their data analysis log, to allow possible sensitivity analysis of the results with and without the modified data.

Summary

- Increased consistency of approach
- Sites are able to fulfill their responsibility for data accuracy
- Service provider is able to support both sites and sponsors
- Sponsor has increased awareness of data changes and their causes
- Sponsor does not have exclusive control over source records
- Re-training opportunities in real time
- Intent of the data originator is preserved

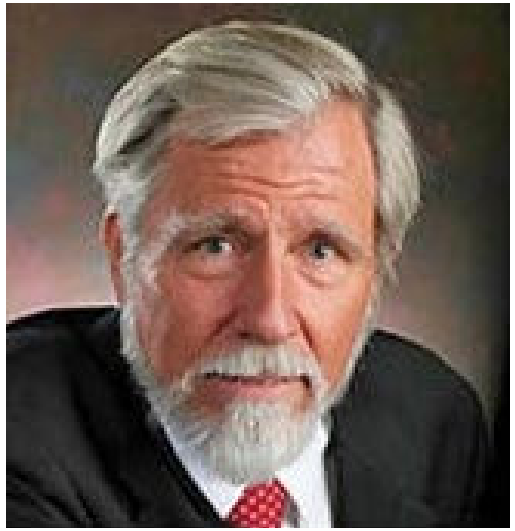
Q & A

Co-Authors

- Patricia Shepherd Delong
- Demian Humler
- Tom Haag
- Alan Yeomans
- Jonathan Andrus
- Sonya Eremenco
- Ashley Finan
- Jonathon Gable
- Derek Gilfillan
- Cindy Howry
- Scottie Kern
- Scott Joseph Lesniewski
- Kelly Simpliciano
- Hannah Staunton
- Jessica Turnbull
- Christina Workman
- Stephen Raymond

Acknowledgments

- Andres Escallon
- Kelly McQuarrie
- Susan Britland
- Bill Byrom
- Adrian Chan
- Celeste A. Elash
- Ilan Halberstam
- Lobo Loo
- Amresh Marunnarkal
- Paul O'Donohoe
- Poh Chiam Sim
- Aman Thukral
- Donna Wauhop
- Jin Zhou



Stephen Raymond, PhD

Thank you for your participation!

Contact Information:

eClinical Forum: info@eclinicalforum.org

Critical Path Institute: eCOAC@c-path.org

CRITICAL PATH
INSTITUTE

Advancing Drug Development.
Improving Lives. Together.

c-path.org