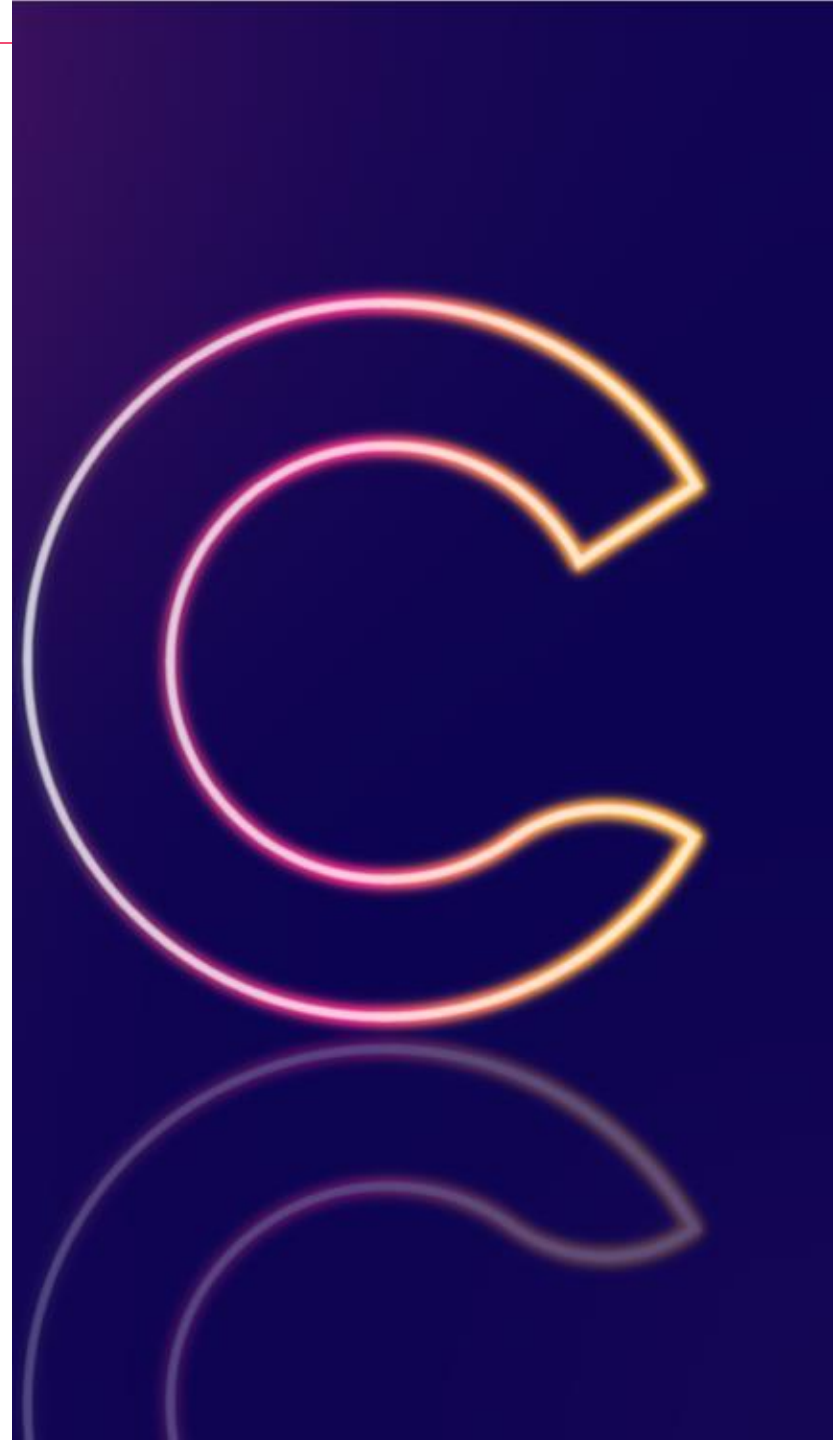




RE06: Real-world Evidence (RE)

The Curious Case of External Controlled Arms (ECAs): Practical Solutions for External and RWD Integration

Manish Deole and Preethi Samala



Disclaimer and Disclosures

- *The views and opinions expressed in this presentation are those of the author(s) and do not necessarily reflect the official policy or position of Cytel or PHUSE.*
- *The author(s) have no real or apparent conflicts of interest to report.*
- *All sensitive information has been anonymized to maintain confidentiality. Our intention is to share our experience working on ECA studies.*

Agenda

01

Why ECA is important

02

Challenges in incorporating ECA and CDISC Package

03

FDA's view

04

Study cases with ECA using RWD

05

Key Takeaways

06

References

01



Why ECA is important

Why ECA is important

Accelerating drug development

- Reduce the need of large control groups which can accelerate trial timelines and regulatory submissions.

Additional usage

- Apart from NDA, this can be used in comparative effective research, Post Marketing studies, label expansion where a randomized trial is not required or feasible.



Trial conduct challenges

- In Rare Disease, Recruitment of Subjects in Randomized control trials is challenging, time-consuming, resource intensive and expensive.
- It is also unethical to administer Placebo Arms in life threatening disease or Conditions.

Existing data for ECA

- Instead, we utilize historical clinical data, natural history studies and Real-world data to supplement or replace control arms.
- RWD may represent more diverse and realistic patient populations, improving external validity of trial results.

02

Challenges in incorporating ECA and CDISC Package



Challenges in incorporating ECA

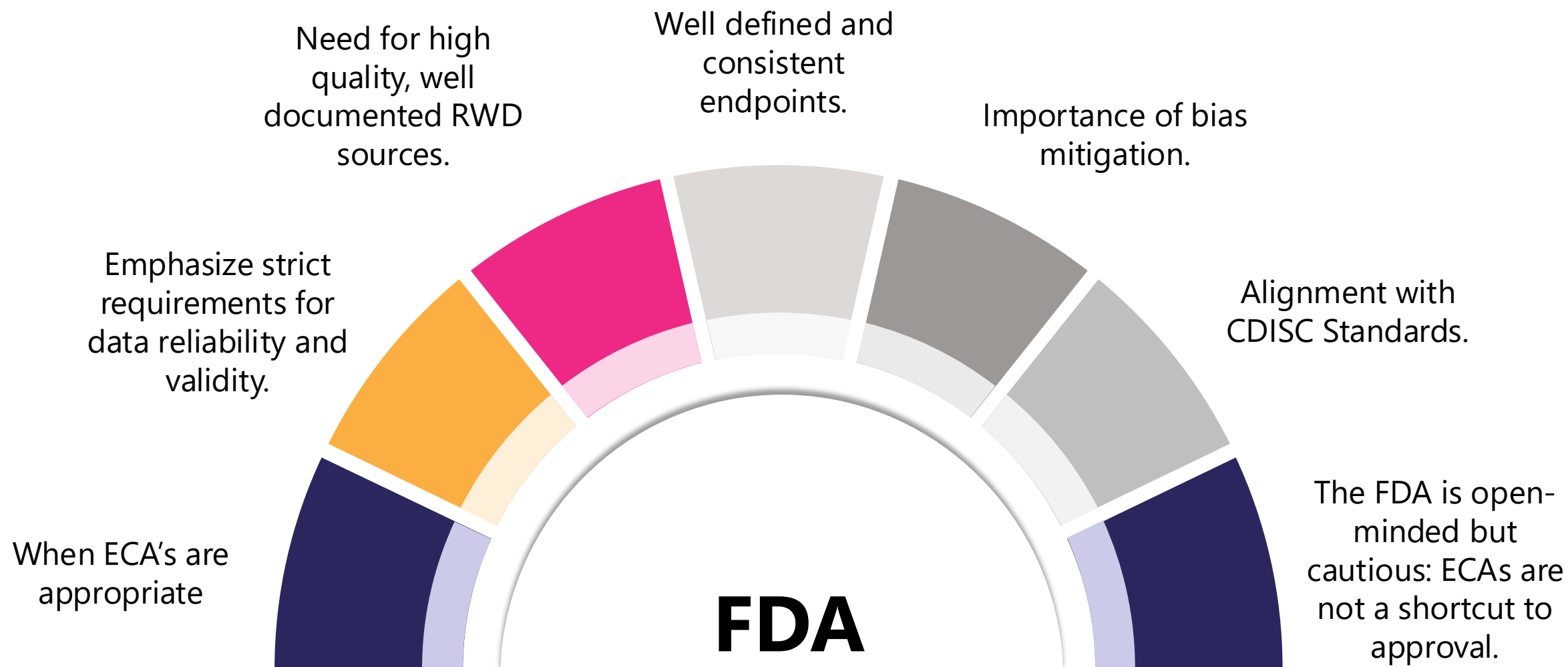


03



FDA's view

FDA view on ECA



04



Study cases with ECA using RWD

Case 1: Use of External Data for Comparison

- **Missing** time points and patient groups.
- **Longer follow-up** comparisons.
- **Patient progression** with / without treatment.
- **Propensity score matching.**

Case 2: Placebo Design and Study Limits

- Placebo with **inactive material** so it would look like the real treatment.
- That small amount **wasn't expected** to have any **clinical effect**.
- **Difficult** to tell true **treatment** effects apart from **placebo** effects.
- This **obscures** the treatment's **true efficacy**, and minor placebo shifts **may skew interpretation**.

Analytical & Technical Challenges



Data Cleaning and Harmonization

- Unclean, missing and partial data.
- Treatment vs. untreated subject data required harmonization.



General Programming

- RWD lacking SDTM compliance demanded careful transformation for ADaM IG alignment.
- Traceability challenges due to non-traditional SDTM structures.



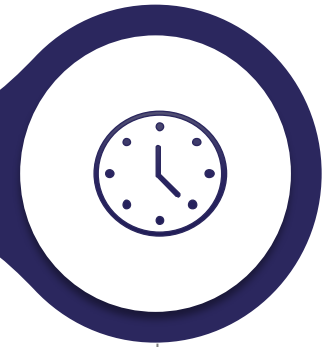
Platform & Runtime Limitations

- Some models took 4–5 hours per figure to run increasing turnaround time for even minor QC errors.



Statistical Modeling Challenges

- Propensity score matching across studies with differing covariate definitions complicated model development.



Regulatory Agility

- Regulatory reviews required rapid responses, versioning, and documentation updates with minimal lead time.

Submission Challenges

Data-sharing hesitancy due to privacy concerns.

Need to **adapt programs** to run securely in **third-party environments**.

Continuous **collaboration** with the sponsor is critical.

Preparedness and **flexibility** are essential

Overall impact:

-Adds **complexity**, increases **risk of bias**, and requires careful **endpoint alignment** before analysis.

05



Key Takeaways

Key Takeaways

RWD → SDTM/ADaM mapping requires **time & custom programming**. **Non-standard structures** often need **custom-made derivations**.

Harmonize terminology across datasets. MedDRA versions, lab units, coding conventions.

Align external data & trial data to CDISC **early**. Ensures **consistency** and **reduces rework** later.

Ensure **full traceability** with strong **documentation**. All assumptions, data limitations, transformation steps, plus define.xml updates.

Watch for **differences across sources**. Visit timing, assessments, missing or partially captured data.

Plan for **extra sensitivity analyses**. Needed due to **variability** and **uncertainty** in external data.

Systematically handle **non-standard formats & missing data**. Apply clear **rules for imputations and transformations**.

Expect additional **regulatory questions**. Be prepared to **justify mapping decisions** and **analytical assumptions**.

06



References

Cytel Blogs

- [External Control Arms: A Powerful Tool for Oncology and Rare Disease Research](#)
- [The Role of External Data in Oncology Drug Development](#)
- [External Control Arms in Drug Development: Methodological and Regulatory Considerations](#)



Current Guidance

Data Standards for Drug and Biological Product Submissions Containing Real-World Data 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)
December 2023
Real-World Data/Real-World Evidence (RWD/RWE)

- RWD as whole
- Focus on **SDTM** only
- Recommendation for **define.xml** and **csdrg**
- Differences in coding system

Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. 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. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Dianne Pearson, 301-796-2500, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

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)
Oncology Center of Excellence (OCE)

February 2023
Real-World Data/Real-World Evidence (RWD/RWE)

- **Type of source for ECA**
e.g., RCT, RWD
- **Access to Data**
- Design Consideration
- Analysis Considerations
- **No CDISC**



Considerations for SDTM Implementation in Observational Studies and Real-World Data

Version 1.0 (Final)

Prepared by the
CDISC Observational Studies & Real-World Data Standards Development Team

Notes to Readers

- This document is based on SDTM v2.0 and SDTMIG v3.4.

Revision History

Date	Version
2024-02-28	1.0 Final

See [Appendix D](#) for Representations and Warranties, Limitations of Liability, and Disclaimers.

- Focus on **SDTM** only
- Cohort, Case Control and **ECA Studies**
- DM / TS consideration for ECA e.g., ARM
- How to handle conformance issues



- Focus on **ADaM** only
- Registry, case-control, etc. can be ECA, but **no specific discussion for ECA**
- Analysis visit Windowing
- Missing Imputation



Thank You

Manish Deole: manish.deole@cytel.com

Preethi Samala: preethi.samala@cytel.com