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Single Day Event

Use of eCOA in Clinical Trials – Programmers' Perspective

Deepthi BM, GSK

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Agenda

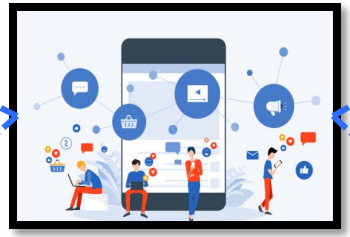
- What are eCOA?
- Applicability of eCOA
- eCOA Setup Process
- eCOA Project Planning
- Data Scenarios
- Missing Data
- Regulatory Consideration

What are eCOA?

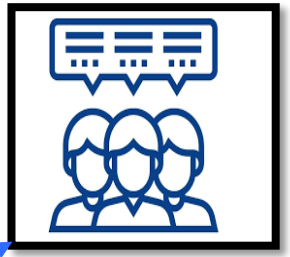
Clinical Outcome Assessment – Assess clinical outcome evaluated by a clinician, a patient, a non-clinician observer or through performance based[1]

Health outcomes reported by a Healthcare Provider after observing health conditions

eClinRO



eCOAs

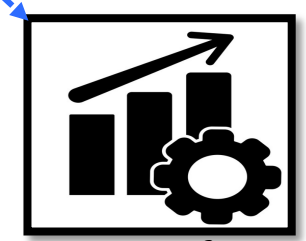


eObsRO

Health outcomes reported by the participant's family or caregiver

Health outcomes reported directly by the patient

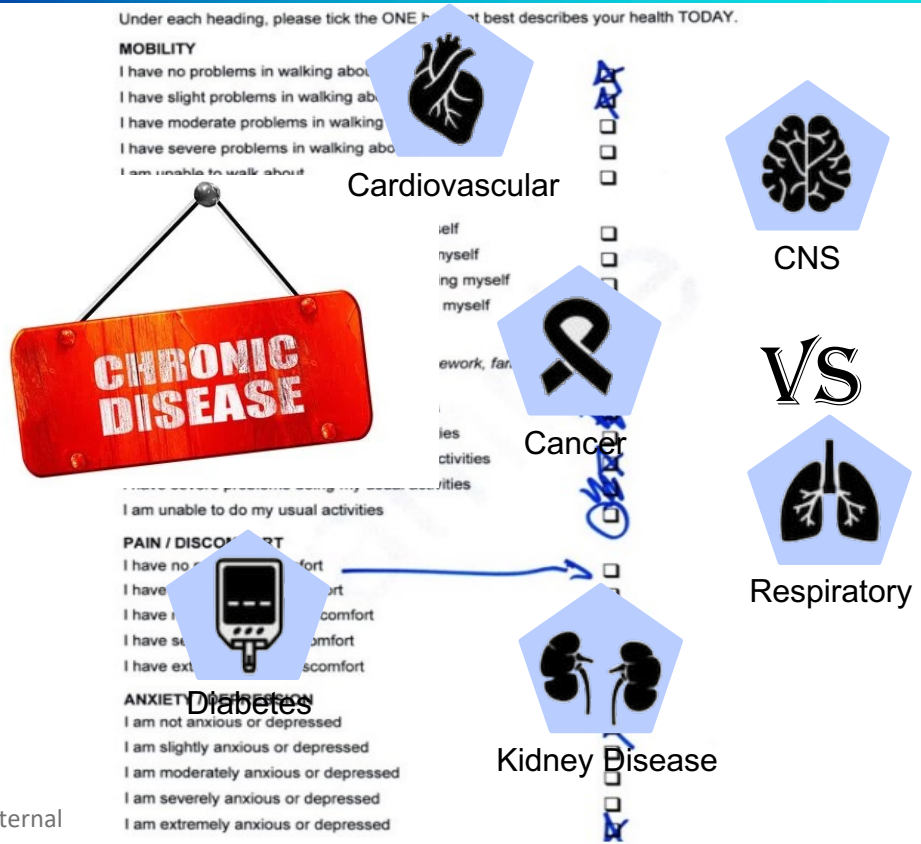
ePRO

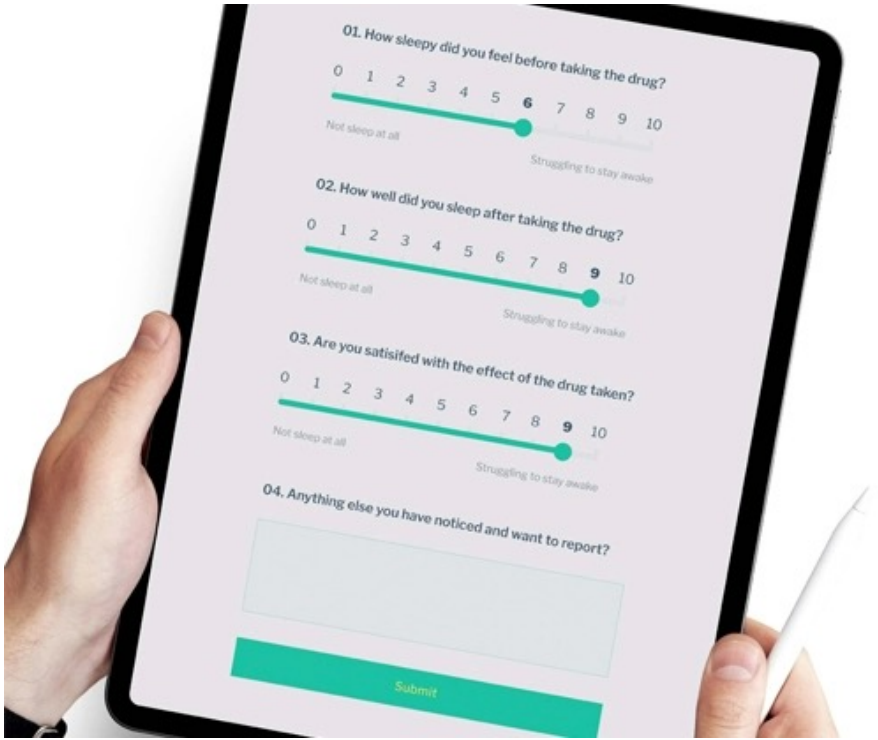


ePerfO

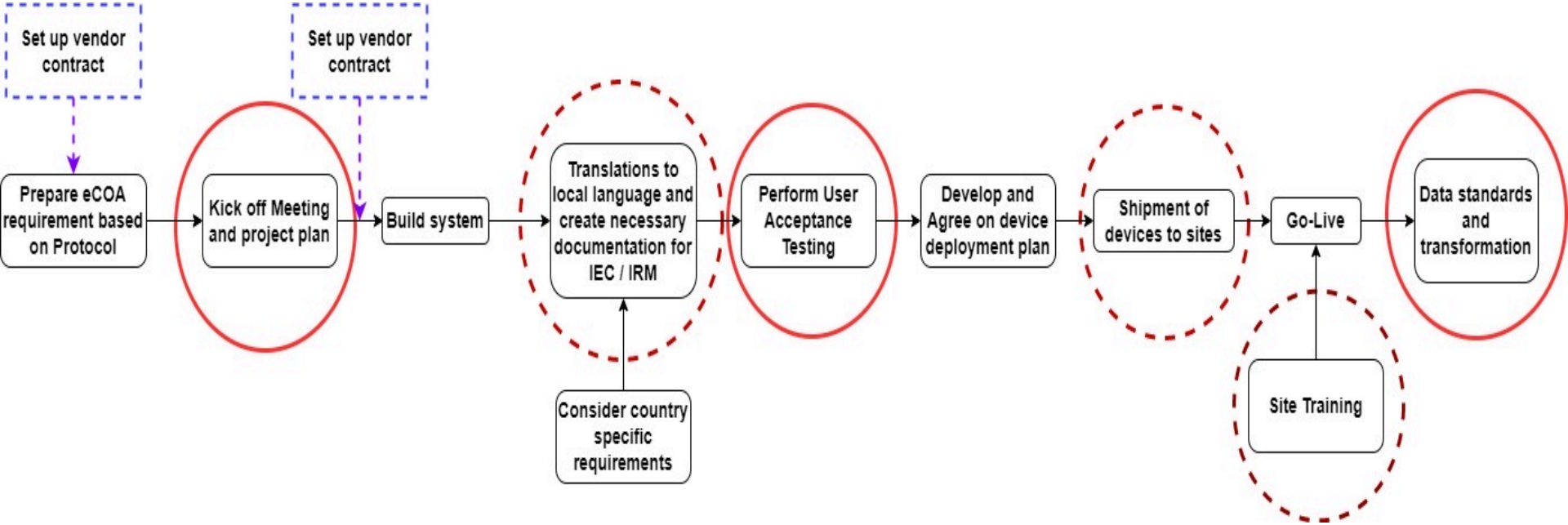
Measurements based on tasks performed by a participant according to instructions administered by HCP.

Applicability of eCOA





eCOA Setup Process – High Level



Programmers should be involved and consulted

Possible areas, if not well conducted, impact programming

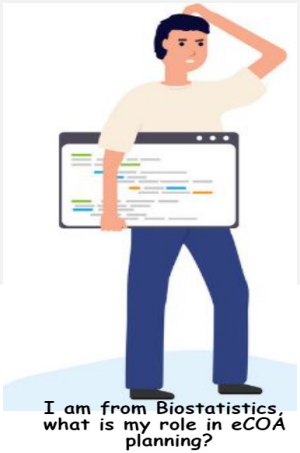
eCOA Project Planning – Involvement of Programmer

- It is important to initiate the eCOA data workflow planning while protocol development is happening
- Involvement of cross functional t… …eting is essential
- All necessary team should par… …eCOA workflow… …stone and timelines

How are the visits / ad-hoc visits handled? How about unscheduled visit?

Are the timepoints correctly captured for daily diary data, meeting analyses requirement?

Is the data collection specified meets the analyses requirement?



Will the design cause missing data and what steps taken to minimize them?

Should we implement eCOA for this assessment?

Data Scenario 1 – Impact to visit slotting algorithm

ACQ-5 assessment is performed at each visit with a +/- 2 days window period

qs.xpt

SUBJID	VISITNUM	QSTESTCD	QSORRES	QSDTC
1001	20	ACQ-01	3	2021-10-10
1001	20	ACQ-02	2	2021-10-10
1001	20	ACQ-03	4	2021-10-10
1001	20	ACQ-04	3	2021-10-10
1001	20	ACQ-05	3	2021-10-10

sv.xpt

SUBJID	VISITNUM	VISIT	SVSTDTC	SVENDTC
1001	20	Visit 20	2021-10-01	2021-10-03

Data Scenario 2 – Translation error

On average, during the past week, how bad were your asthma symptoms when you **woke up in the morning**? 0 = no symptoms 1 = very mild symptoms 2 = mild symptoms 3 = moderate symptoms 4 = quite severe symptoms 5 = severe symptoms 6 = very severe symptoms	औसतन, पिछले सप्ताह के दौरान, आपके अस्थमा के लक्षण कितने बुरे थे जब **आप रात में जागते थे प्रभात**? 0 = कोई लक्षण नहीं 1 = बहुत हल्के लक्षण 2 = हल्के लक्षण 3 = मध्यम लक्षण 4 = काफी गंभीर लक्षण 5 = गंभीर लक्षण 6 = बहुत गंभीर लक्षण

- Identified the issue lately
- Data cannot be changed hence assumed to be missing for analyses
- Impact to programming logic

Data Scenario 3 – Duplicate records due to device synchronization issue

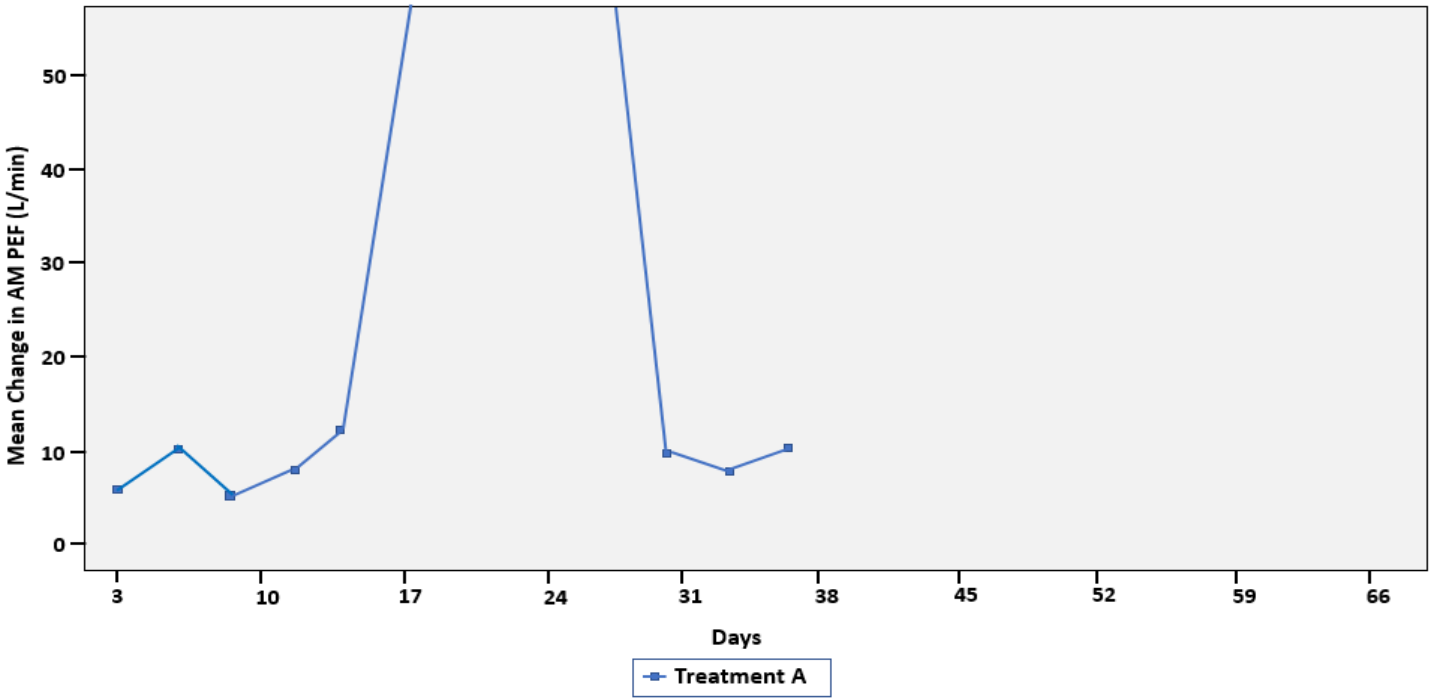
SUBJID	RETESTCD	REORRES	REORRESU	REDTC	RETPTN
1001	PEF	350	ml	2017-07-01T10:00	1
1001	PEF	350	ml	2017-07-01T10:00	1
1001	PEF	348	ml	2017-07-01T18:00	2
1001	PEF	348	ml	2017-07-01T18:00	2

Listings were impacted as programs were developed considering one record per subject, per parameter, per timepoint

Data Scenario 4 – When device was replaced

Protocol: xxxxxxxx
Population: Intent-to-Treat

Figure x.x
Mean Change from Baseline in AM PEF(L/min) On- and Post- Treatment



Missing Data – A big pain point for analyses

- Missing data can lead to bias and lack of precision in statistical analyses
- Types of missing data (*Rubin 1976*)

I. Missing Completely at Random (MCAR): No relationship between the pattern of missing data
II. Missing at Random (MAR): Has a relationship with observed but not to a missing data
III. Missing Not at Random (MNAR): Has a relationship on how data is missing. Difficult to know the true nature of missing data

- Ways of dealing with missing data, recently most used and widely accepted is **Multiple Imputation**
- Creates multiple predictions for each missing value, considered uncertainty in the imputations and yield more accurate standard errors

Handling missing data - Multiple Imputation Process

Reference: CDSIC Analysis Data Model Implementation Guide

Step 1: Multiple Imputation

Create multiple dataset in which all plausible values for each missing data are imputed. SAS procedure used is PROC MI, created the dataset containing multiple imputation including original data. The iterations are indexed with the variable _IMPUTATION_

Step 2: Analyze

The analyses of the output dataset from Step 1 can be done using any desired statistical procedure and capture the resulting statistical estimates

Step 3: Combine to generate result

These estimates are based on the pooling of estimates from the multiple imputation dataset that are used to evaluate statistical significance. PROC MIANALYZE combines the result from every _IMPUTATION_ iteration created using MI procedure

Multiple Imputation – Data submission

Reference: CDSIC Analysis Data Model Implementation Guide

In ADaM, the documentation of derived variables via variable level metadata, and statistical results via analysis results metadata, is paramount to achieving the concept of traceability. However, documenting the traceability of estimates created via multiple imputation cannot be achieved with these current metadata methods. In addition, it would not be practical to include all datasets that are created from the PROC MI process as part of a submission. To address traceability, the ADaM recommendation is to provide the program statements from the 3 procedures mentioned above as a part of the analysis results metadata. This allows the reviewer to re-create the analysis as desired. Of primary importance is to ensure that the options used in PROC MI—specifically the value of the seed, the number of iterations, and the method used for imputation—are clearly denoted.

- Multiple Imputation procedure takes time to run
- Ideal way is to create the imputation dataset for output generation
- This also helps for pooled analyses (ISE)
- Refer 2022 CDSIC EU Connect ADaM Traceability https://wiki.cdisc.org/display/ITAUG/2022-06-29?preview=%2F153066587%2F153066585%2F2022-CDISC-Eu-ADaMTraceability-SFaini.pdf

Regulatory Considerations

- FDA recommendation to implement backup plan if there are any malfunctions with the electronic devices
- FDA recommendation to reduce variations in instrument format and functionality from one device to another in case of BYOD usage
- Sponsor should develop separate device-related respondent instructions and training materials for FDA review while switching from paper to electronic data collection mode
- Sponsor should also submit equivalency test result to support measurement equivalence between paper and electronic COAs
- Sponsor should submit any device usability testing and result, screen shot of the instrument, site training materials, **Raw score** if collected and **Derived score** in SDTM and ADaM

References

(1) FDA: Methods to Identify What is Important to Patients & Select, Develop or Modify Fit-for-Purpose Clinical Outcomes Assessments https://www.fda.gov/media/116277/download

(2) FDA: Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims https://www.fda.gov/media/77832/download

(3) FDA's Roadmap to Patient Focused Outcome Measurement in Clinical Trials https://nationalhealthcouncil.org/webinars/coa-series-fdas-roadmap-to-patient-focused-outcome-measurement-in-clinical-trials/

(4) Validation and equivalence of electronic clinical outcomes assessment systems, International Journal of Clinical Trials, *Gary ST et al. Int J Clin Trials. 2020 Nov;7(4):271-277* http://www.ijclinicaltrials.com

(5) Xtalks, Data Standards for eCOA in Clinical Trials https://xtalks.com/webinars/data-standards-for-ecoa-in-clinical-trials/

phuse

The Global Healthcare Data Science Community

Contact Channels
UK +44 1843 609600
office@phuse.global
phuse.global

Social Media
@phusetwitta
/phusebook
/phusetube
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