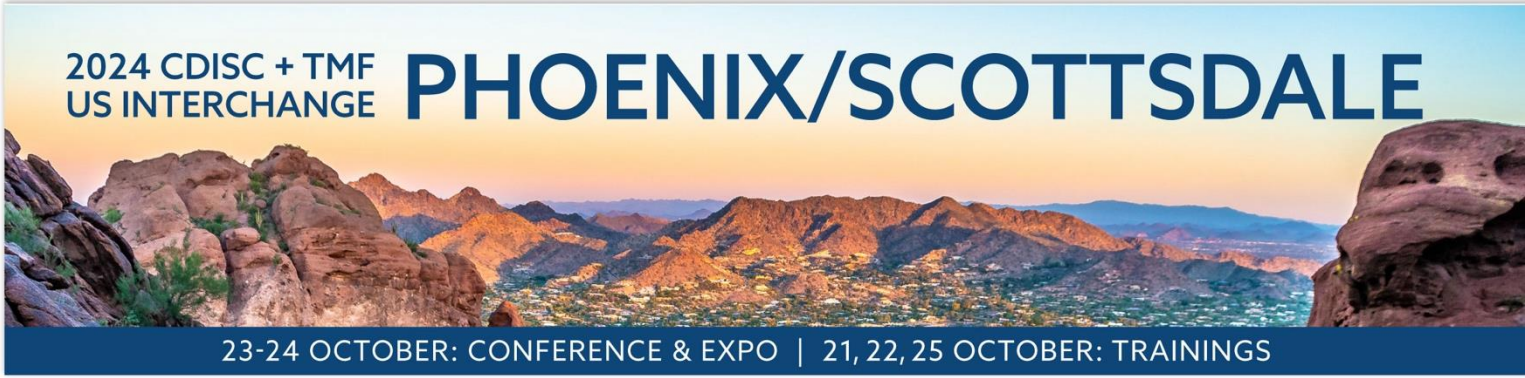



# Applying guidance from "Submitting Patient-Reported Outcome Data in Cancer Clinical Trials" as a best practice for COA data and analysis in non-cancer studies

Presented by Charity Quick, Director, Statistical Programming, Emergent BioSolutions

# Meet the Speaker

## Charity Quick

Title: Director, Statistical Programming

Organization: Emergent BioSolutions

Charity Quick is the Director of Statistical Programming at Emergent BioSolutions.
Her experience involves almost 2 decades of regulatory submissions programming and CDISC conversions for all phases of work as well as managing, mentoring, and training Statistical Programmers.
In addition to her passion for Data Standards, Charity enjoys music, film, gardening, and serving on the board of a local NC canine rescue.

# 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 CDISC.*

- *The author(s) have no real or apparent conflicts of interest to report.*

# Agenda

1. Goals of the Presentation
2. FDA/CDISC PRO data collection, analysis, and review landscape
3. “Submitting PRO Data in Cancer Clinical Trials” Highlights for SDTM and ADaM data preparation
4. Incorporating PROCCT into SDTM QS and ADaM ADQS Best Practices
5. Conclusion

# Definitions

## COA definition

"an assessment of a clinical outcome that describes or reflects how an individual feels, functions or survives. The assessment can be made through report by a clinician, a patient, a non-clinical observer, or through a performance-based assessment."

## 4 types of COAs

- 1. patient-reported outcome (PRO)
- 2. clinician-reported outcome (ClinRO)
- 3. observer-reported outcome (ObsRO)
- 4. performance outcome (PerfO)

** from the FDA CDER SBIA Webinar Series 2017*
*https://sbiaevents.com/files/DS-Webinar-Nov-2017.pdf*

# Presentation Goals

# Presentation Goals

## Establish Importance of clear PRO data processing for analysis and FDA regulatory review

## Provide Practical Guidance for creating PRO based CDISC deliverables for FDA review

- Assemble recommendations from various industry publications
- Introduce relevant content and examples included in new “Submitting Patient-Reported Outcome Data in Cancer Clinical Trials” (PROCCT)
- Setting the stage for success with data, documentation, and vendor selection

# FDA/CDISC PRO data collection, analysis, and review landscape

Putting the Pieces Together as Standards Rapidly Evolve

# Increasing Details and Specificity requested in Guidance

## 2015 to 2020

**ADaM IG versions include a section titled**
**“Adding Records to Create a Full Complement of Analysis Timepoints for Every Subject”**

Mentions using PHANTOM records as an option that the ADaM team neither encourages or discourages – wording hasn’t changed through IG versions

“PHANTOM” added to DTYPE codelist in 2020

**FDA sdTCG Oct 2017**

Some items in an instrument may be logically skipped per the instrument’s instructions. Responses for logically skipped items should be (1) recorded and/or scored according to the instructions provided in the instrument’s user manual, scoring manual, or other documentation provided by the instrument developer and (2) included in the submission dataset.

**FDA Webinar Oct 2017**

| | | |
|---|---|---|
| Highlighted Need for COA PRO data to include Logically Skipped items in SDTM and carried into ADaM | Used several different QRS instruments as examples – notably the WPAI-SHP V2.0 | Emphasized need for traceability for missing data and the importance of 21 CFR guidance on instruments and subject response reliability |

# Increasing Details and Specificity requested in Guidance

## 2020 to 2024

### SDTM IG V3.4 (2021)

### 2 updates to language in “Tests Not Done” Section 4.5.1.2

1. If the data on the CRF is missing and "Yes/No" or "Done/Not Done" was not explicitly captured, a record should not be created to indicate that the data was not collected, with the exception of QRS. Regulatory agencies may require a record for all items on a CRF in QRS datasets (e.g., FT, QS, and clinical classifications in RS).
2. If a record is created for a test not done, --REASND is populated only if a reason was explicitly collected except for QRS logically skipped items.

### Updates to some QRS Supplements to add guidance for missing/skipped items

### Using the WPAI-SHP V2.0 as an example

Data Tabulation examples updated to include items that were skipped

The term “logically skipped” was replaced with “Conditional Branching” and introduces QSCBRFL

Indicates that we may see more information in SDTM IG V4.0 pertaining to

### Detailed collection, tabulation, and analysis guidance for PROs in other FDA publications

“Submitting Patient-Reported Outcome Data in Cancer Clinical Trials” published in Nov 2023 to supplement the PFDD Guidance Series

# “Submitting Patient-Reported Outcome Data in Cancer Clinical Trials” (PROCCT) Highlights for SDTM and ADaM data preparation

Non-Binding FDA Recommendations

# PROCCT relevance to non-cancer studies

- **Scope does specify that it is intended for "cancer" studies but the examples and specifications are largely not cancer specific**
- **Outside of a specific QRS Supplement, the details provided in the PROCCT are more comprehensive than many other documents**
  - QS SDTM examples
  - ADQS ADaM examples
- **The PROCCT could be seen as an indicator of future direction of standard for PRO data collection, tabulation, and analysis**
- **Although PROCCT guidance focuses on PRO measures, some of these recommendations may be relevant to other COAs**

# PROCCT SDTM

## General Guidance

- Follow CDISC IG and QRS (if available)
- **QSTEST/CD** - name according to CDISC CT and QRS(if available)
- Additional collected content instructions -
  - Items such as instrument language, data collector, mode of administration can be added to SUPPQS or as QSTEST/CD rows
  - Bring additional content into ADaM only if there is an analysis need for it

# PROCCT SDTM

## SDTM Record Level Completeness Expectation:

"The QS dataset should include one record per item per PRO measure per patient per assessment timepoint, regardless of whether an item response is missing"

### How to Populate Missing or Logically Skipped data records

| Missing Data | Logically Skipped | Computerized Adaptive Testing (CAT) |
|---|---|---|
| Detailed Table outlining how to populate QSREASND based on 4 different scenarios | Use sdTCG guidance to ensure that QS contains logically skipped items with appropriate QSSTAT, QSREASND, and QSORRES | Do NOT create additional records for CAT |

# PROCCT Recommended QS Representation of Missing PRO Data

| Scenario | Recommended Representation in QS Dataset |
|---|---|
| The patient did not respond to an item administered within a PRO measure. | The row for the missing item response should include:<br>• QSSTAT = 'NOT DONE'<br>• QSREASND contains the reason the patient did not respond if known/collected. Otherwise, QSREASND is empty/null. |
| A source data summary score cannot be calculated per the scoring algorithm based on the available item responses (e.g., due to insufficient item response data). | The row for the missing source data summary score should include:<br>• QSSTAT = 'NOT DONE'<br>• QSREASND is populated if known/collected (e.g., QSREASND = 'NOT CALCULABLE'). Otherwise, QSREASND is empty/null. |
| The patient was not administered the PRO measure either at an onsite visit attended by the patient or at a planned (per protocol) offsite PRO assessment timepoint. | The row for each missing item response and source data summary score within the measure should include:<br>• QSSTAT = 'NOT DONE'<br>• QSREASND contains the reason the measure was not administered if known/collected. Examples include, but are not limited to, patient was physically unable to complete the PRO measure due to adverse event, patient refusal, patient did not provide, study site failed to administer or other site staff error, or technological problems with a PRO administered electronically. |
| The patient did not attend an onsite visit and the PRO measure is only administered onsite. | The row for each missing item response and source data summary score within the measure should include:<br>• QSSTAT = 'NOT DONE'<br>• QSREASND contains the reason the patient did not attend the visit if known/collected. Examples include, but are not limited to, patient was unable to attend a scheduled trial visit due to hospitalization. |

# SDTM example for Missing Data

| Row | USUBJID | VISIT | QSCAT | QSTEST | QSTESTCD | QSORRES | QSSTAT | QSREASND | QSDTC |
|---|---|---|---|---|---|---|---|---|---|
| 1 | A_100_1 | SCREENING | Measure Name and Version | I01-Item 1 | I01 | 3 | | | 2022-02-01 |
| 2 | A_100_1 | SCREENING | Measure Name and Version | I01-Item 2 | I02 | 5 | | | 2022-02-01 |
| 3 | A_100_1 | CYCLE 1 DAY 1 | Measure Name and Version | I01-Item 1 | I01 | | NOT DONE | | 2022-02-22 |
| 4 | A_100_1 | CYCLE 1 DAY 1 | Measure Name and Version | I01-Item 2 | I02 | 4 | | | 2022-02-22 |
| 5 | A_100_1 | CYCLE 2 DAY 1 | Measure Name and Version | I01-Item 1 | I01 | 2 | | | 2022-03-15 |
| 6 | A_100_1 | CYCLE 2 DAY 1 | Measure Name and Version | I01-Item 2 | I02 | 4 | | | 2022-03-15 |
| 7 | A_100_1 | CYCLE 3 DAY 1 | Measure Name and Version | I01-Item 1 | I01 | | NOT DONE | PATIENT REFUSAL | 2022-04-05 |
| 8 | A_100_1 | CYCLE 3 DAY 1 | Measure Name and Version | I01-Item 2 | I02 | | NOT DONE | PATIENT REFUSAL | 2022-04-05 |
| 9 | A_100_2 | SCREENING | Measure Name and Version | I01-Item 1 | I01 | 4 | | | 2022-03-14 |
| 10 | A_100_2 | SCREENING | Measure Name and Version | I01-Item 2 | I02 | 5 | | | 2022-03-14 |
| 11 | A_100_2 | CYCLE 1 DAY 1 | Measure Name and Version | I01-Item 1 | I01 | | NOT DONE | HOSPITALIZATION | |
| 12 | A_100_2 | CYCLE 1 DAY 1 | Measure Name and Version | I01-Item 2 | I02 | | NOT DONE | HOSPITALIZATION | |

# PROCCT SDTM

## Clarifying use of PROCCT by identifying use in SDTM TS Domain

**TSPARAMCD = ‘FDATCHSP’**
**TSPARAM = ‘FDA Tech Spec’**
**TSVAL = ‘Oncology PROs Technical Specifications Guidance v1.0’**

# PROCCT ADaM

## General Guidance

- ADQS should be derived from SDTM QS as well as any other ADaM or SDTM data needed
- ADQS must contain treatment assignment, stratification, subgrouping, and other covariates needed for analysis
- ADQS must have all individual item scores and summary scores (e.g., subscale scores, total scores, other composite or index scores) that will be used for analysis

## ADaM Variables

- **PARCATy** – many details about use of PARCATy including 5 examples.
- **DTYPE** = “PHANTOM” is used to represent missing item scores or summary scores such that each patient has the same number of observations

# ADaM example for PARCATy use

| PARCAT1 | PARCAT2 | PARCAT3 | PARCAT4 | PARCAT5 | PARAM |
|---|---|---|---|---|---|
| Measure Name and Version | ITEM | Subscale Score 1 | Scale Score A | Scale Score B | Item 1 |
| Measure Name and Version | ITEM | Subscale Score 1 | Scale Score A | Scale Score B | Item 2 |
| Measure Name and Version | ITEM | Subscale Score 1 | Scale Score A | Scale Score B | Item 3 |
| Measure Name and Version | ITEM | Subscale Score 2 | Scale Score A | Scale Score B | Item 4 |
| Measure Name and Version | ITEM | Subscale Score 2 | Scale Score A | Scale Score B | Item 5 |
| Measure Name and Version | ITEM | Subscale Score 3 | Scale Score A | | Item 6 |
| Measure Name and Version | SUBSCALE SCORE | Subscale Score 1 | Scale Score A | Scale Score B | Subscale Score 1 |
| Measure Name and Version | SUBSCALE SCORE | Subscale Score 2 | Scale Score A | Scale Score B | Subscale Score 2 |
| Measure Name and Version | SUBSCALE SCORE | Subscale Score 3 | Scale Score A | | Subscale Score 3 |
| Measure Name and Version | SCALE SCORE | | Scale Score A | | Scale Score A |
| Measure Name and Version | SCALE SCORE | | | Scale Score B | Scale Score B |

# PROCCT ADaM

## ADaM Variables (continued)

- **ONTRTFL** and **ONTRxxFL** – used to specify whether the observation occurred while the patient was on treatment (or on trt during a particular period xx) – STRONGLY RECOMMENDED
- **SCBLFL** - used on the ABLFL = “Y” record to indicate that baseline is sourced from a Screening assessment timepoint(s) rather than from a prespecified baseline assessment timepoint
- **PROEXPFL** - indicator variable to specify whether the PRO parameter (item or summary score) corresponds to a per protocol planned PRO assessment timepoint. Use of **PROEXPFL** will be based on the intended PRO use (clinical benefit vs safety/tolerability). If PRO use is both, use **PROEX1FL** and **PROEX2FL**
- **PROSCMFL -** indicator variable to specify whether the PRO item score or summary score is populated at a planned (per protocol) PRO assessment timepoint. Empty if AVAL/AVALC are missing and response not provided by patient

# PROCCT ADaM

## ADaM Variables (continued)

- **AREASND** – use when the item or summary score is missing. Populated from SDTM QS data QSREASND if the record comes from SDTM. Otherwise, **AREASND** is populated by another source, when available. For example, if the PRO data are used to evaluate clinical benefit, **AREASND** may be populated for phantom records using DS.DSDECOD or ADSL.DCTREASP for a patient who died or discontinued from treatment

## Other variables to include in ADQS

| Variables from ADSL | Variables from SDTM QS |
|---|---|
| DTHDT, ESODT, ESSTT, DCSREAS, EOTDT, EOTSTT, DCTREAS, TRTDURD, TRxxDURD, RANDDT, RANDFL, SAFFL, ITTFL | QSSEQ, VISIT, VISITNUM, QSSTAT, QSREASND |

# PROCCT ADaM

## Missing data approaches in ADaM

- Copied from SDTM QS where the QS domain has NOT DONE item records for items
- Derive DTYPE="PHANTOM" records in ADQS
  - QSSTAT and QS.QSREASND are null for phantom records derived in the ADQS dataset
  - PHANTOM records should only be derived when the row representing the missing item score or source data summary score does not exist in SDTM QS.
  - When PHANTOM records are derived in the ADQS dataset for an entire PRO measure, a row should be derived for each item and summary score within the PRO measure, with the reason populated in ADQS.AREASND (if known) and distributed across all rows.

# PROCCT ADaM

## Missing data scenarios for adding records in ADaM

| PRO for Clinical Benefit | PRO for Safety/Tolerability |
|---|---|
| • ADQS should have a record for every item and sub-score for every per protocol timepoint for a patient that was randomized.<br>• Include rows for patients that were randomized but not treated.<br>• ADQS should contain rows for subjects even after intercurrent events.<br>• If patient pauses treatment, PHANTOM rows should be added for timepoints during the pause | • ADQS should have a record for every item and sub-score for every per protocol timepoint for a patient that was treated.<br>• ADQS should contain rows for subjects up until Intercurrent Events. Rows can be added after Intercurrent Events but the guidance advises reducing patient burden by not doing so.<br>• If patient pauses treatment, PHANTOM rows should be added for timepoints during the pause |

Intercurrent Events - Events that occur post randomization in randomized control trials that can alter the course of the trial and jeopardize evaluation and decision making in regulatory science. Treatment Discontinuation, Death, and Disease Progression are examples of Intercurrent Events.

# ADaM example for Missing Data

| USUBJID | VISIT | AVISIT | PARCAT1 | PARAM | PARAMCD | AVAL | QSSTAT | QSREASND | DTYPE | AREASND | DCTREAS | PROEXPFL | PROSCMFL | ONTRTFL |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| A_100_1 | SCREENING | SCREENING | Measure Name and Version | I01-Item 1 | I01 | 3 | | | | | | Y | Y | |
| A_100_1 | SCREENING | SCREENING | Measure Name and Version | I01-Item 2 | I02 | 5 | | | | | | Y | Y | |
| A_100_1 | SCREENING | SCREENING | Measure Name and Version | Total Score | TS | 8 | | | | | | Y | Y | |
| A_100_1 | CYCLE 1 DAY 1 | BASELINE | Measure Name and Version | I01-Item 1 | I01 | | NOT DONE | | | | | Y | | Y |
| A_100_1 | CYCLE 1 DAY 1 | BASELINE | Measure Name and Version | I01-Item 2 | I02 | 4 | | | | | | Y | Y | Y |
| A_100_1 | CYCLE 1 DAY 1 | BASELINE | Measure Name and Version | Total Score | TS | | | | | NOT CALCULABLE | | Y | | Y |
| A_100_1 | CYCLE 2 DAY 1 | CYCLE 2 DAY 1 | Measure Name and Version | I01-Item 1 | I01 | 2 | | | | | | Y | Y | Y |
| A_100_1 | CYCLE 2 DAY 1 | CYCLE 2 DAY 1 | Measure Name and Version | I01-Item 2 | I02 | 4 | | | | | | Y | Y | Y |
| A_100_1 | CYCLE 2 DAY 1 | CYCLE 2 DAY 1 | Measure Name and Version | Total Score | TS | 6 | | | | | | Y | Y | Y |
| A_100_1 | CYCLE 3 DAY 1 | CYCLE 3 DAY 1 | Measure Name and Version | I01-Item 1 | I01 | | NOT DONE | PATIENT REFUSAL | | PATIENT REFUSAL | | Y | | Y |
| A_100_1 | CYCLE 3 DAY 1 | CYCLE 3 DAY 1 | Measure Name and Version | I01-Item 2 | I02 | | NOT DONE | PATIENT REFUSAL | | PATIENT REFUSAL | | Y | | Y |
| A_100_1 | CYCLE 3 DAY 1 | CYCLE 3 DAY 1 | Measure Name and Version | Total Score | TS | | | | | PATIENT REFUSAL | | Y | | Y |
| A_100_2 | SCREENING | SCREENING | Measure Name and Version | I01-Item 1 | I01 | 4 | | | | | | Y | Y | |
| A_100_2 | SCREENING | SCREENING | Measure Name and Version | I01-Item 2 | I02 | 5 | | | | | | Y | Y | |
| A_100_2 | SCREENING | SCREENING | Measure Name and Version | Total Score | TS | 9 | | | | | | Y | Y | |
| A_100_2 | CYCLE 1 DAY 1 | BASELINE | Measure Name and Version | I01-Item 1 | I01 | | NOT DONE | HOSPITALIZATION | | HOSPITALIZATION | | Y | | |
| A_100_2 | CYCLE 1 DAY 1 | BASELINE | Measure Name and Version | I01-Item 2 | I02 | | NOT DONE | HOSPITALIZATION | | HOSPITALIZATION | | Y | | |
| A_100_2 | CYCLE 1 DAY 1 | BASELINE | Measure Name and Version | Total Score | TS | | | | | HOSPITALIZATION | | Y | | |
| A_100_2 | CYCLE 2 DAY 1 | CYCLE 2 DAY 1 | Measure Name and Version | I01-Item 1 | I01 | | | | PHANTOM | DEATH | DEATH | | | |
| A_100_2 | CYCLE 2 DAY 1 | CYCLE 2 DAY 1 | Measure Name and Version | I01-Item 2 | I02 | | | | PHANTOM | DEATH | DEATH | | | |
| A_100_2 | CYCLE 2 DAY 1 | CYCLE 2 DAY 1 | Measure Name and Version | Total Score | TS | | | | PHANTOM | DEATH | DEATH | | | |
| A_100_2 | CYCLE 3 DAY 1 | CYCLE 3 DAY 1 | Measure Name and Version | I01-Item 1 | I01 | | | | PHANTOM | DEATH | DEATH | | | |
| A_100_2 | CYCLE 3 DAY 1 | CYCLE 3 DAY 1 | Measure Name and Version | I01-Item 2 | I02 | | | | PHANTOM | DEATH | DEATH | | | |
| A_100_2 | CYCLE 3 DAY 1 | CYCLE 3 DAY 1 | Measure Name and Version | Total Score | TS | | | | PHANTOM | DEATH | DEATH | | | |

# Incorporating PROCCT into SDTM QS and ADaM ADQS Best Practices

Recommendations for data, documentation, and vendor selection

# From the PROCCT

**“Understanding the reasons for and prevalence of missing PRO data are critical to support FDA review and regulatory decision-making.”**

# SDTM Recommendations

**Best Practice – Unless contradicted by the QRS Supplement being used or the PRO instrument is a CAT, QS should include a record for each subject, item, and timepoint expected per protocol for the PRO instrument.**

- Follow sdTCG for Logically Branched items and follow PROCCT for other missing items
- Optional addition of records in QS after intercurrent events and/or during treatment pauses, but those might be better left to ADaM ADQS using PHANTOM records and AREASND
- Choosing a vendor that will provide source PRO data that already includes logically skipped and missing items will greatly reduce the time, cost, and error prone task of manually adding these rows into SDTM although, some data manipulation may still be needed for QSREASND
- If following PROCCT guidance, Include a row in SDTM TS as shown in the PROCCT and this presentation

# SDTM Recommendations

**Best Practice – With the exception of derived scores to be completed in ADaM, ensure that additional information for analysis, traceability, and regulatory review are added to data or supporting documentation.**

- The study acrf.pdf should include PRO data screens if those data were not transcribed into the CRF. Append these to the acrf.pdf but the origin of those fields in the define.xml is still “eDT”.
- Ensure that you have chosen a PRO vendor that can easily provide data collection screens for annotation.
- For ease of review and analysis use, consider creating separate QS domains for each instrument. It is not necessary to “split” QS only when the size exceeds limits. See CDISC MSG 2.0 for examples of split QS domains in the acrf.pdf and define.xml.
- As described in the PROCCT, include additional collected items pertaining to the PRO in SUPPQS or as rows in the QS domain.

# ADaM Recommendations

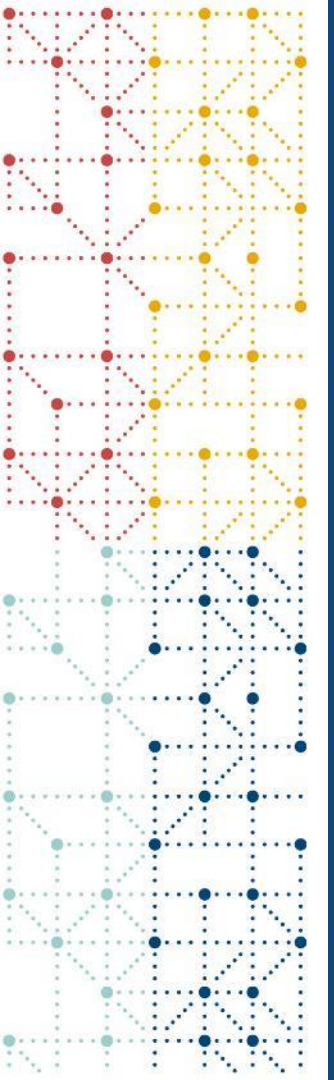
**Best Practice – Unless contradicted by the QRS Supplement being used or the PRO, ADQS should include a record for each subject, item, and timepoint expected per protocol for the PRO instrument.**

- Use PROCCT guidance to add PHANTOM rows based on how the PRO is to be utilized in the trial (clinical benefit vs safety/tolerability)
- Ensure that records added for missing data will meet all study analysis needs so that further manipulation of data is not needed in Table and Figure programs
- Follow PROCCT guidance for correct use of AREASND to describe the reason why the item or sub-score was not performed

# ADaM Recommendations

**Best Practice – Ensure that variables and variable content included in ADQS address all analysis needs and any potential regulatory review needs.**

- Use PROCCT recommendations about what variables from study ADSL and SDTM QS are needed in ADQS
- If details about the correct use of PARCATy variables are not present in a QRS Supplement or CDISC CT for the PRO, follow PROCCT guidance about populating PARCATy to provide accurate information about items and sub-scores
- Add additional ADaM flag variables present in PROCCT guidance – ONTRTFL, PROEXPFL, PROSCMFL, SCBLFL, AREASND



# Conclusion

Final Thoughts

# From the FDA “Submitting Patient-Reported Outcome Data in Cancer Clinical Trials”

**“Understanding the reasons for and prevalence of missing PRO data are critical to support FDA review and regulatory decision-making.”**

# Final Thoughts

**Standards pertaining to COA/PRO are rapidly evolving**

**FDA has made it clear that clear traceability pertaining to subject response data – particularly with missing items – is expected**

**When it comes to QS and ADQS, NOT DONE, Logically Skipped and Phantom records should be incorporated the dataset level moving forward even though this isn't fully part of the standard in all guidance documents**

**Additional details added via variables, define, acrf are recommended**

**Choosing Quality PRO Vendors that provide the full framework of items (including those missing and logically skipped) is advised to avoid the need for time consuming manual work at the SDTM level**

# Thank You!

**Contact me:**
Charity Quick
Emergent BiosSolutions, Inc
quickc@ebsi.com

**Sources used:**

From CDISC
CDISC Metadata Submission Guidelines v2.0
SDTM Implementation Guides
ADaM Implementation Guides
QRS Supplements – specifically WPAI-SHP v2.0

From FDA
“Submitting Patient-Reported Outcome Data in Cancer Clinical Trials”
“Study Data Technical Conformance Guide”
FDA CDER SBIA Webinar Series 2017

Recommended Reading
PharmaSUG 2023 - Paper DS-051
“The Phantom of the ADaM: Adding Missing Records to BDS Datasets”
Anastasiia Drach, Intego Group