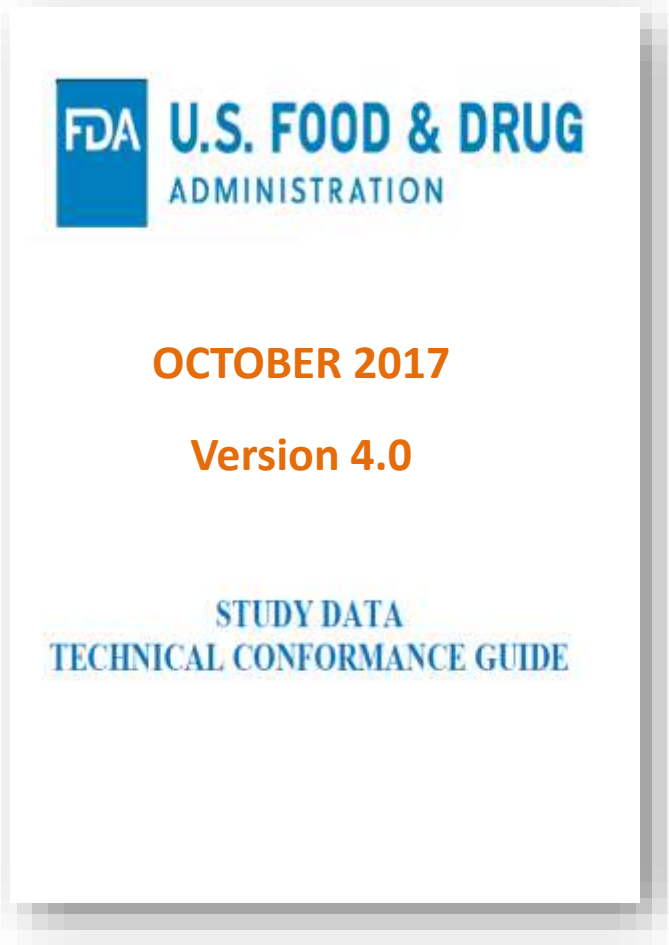
U.S. FOOD & DRUG ADMINISTRATION

Study Data Technical Conformance Guide (TCG)

Webinar Series
2017

Center for Biologics Evaluation and Research (CBER)
Center for Drug Evaluation and Research (CDER)

The TCG



- **TCG** provides recommendations on *how* to submit required standardized study data.
- **TCG** is non-binding, but adherence to the recommendations facilitates regulatory review.
- **TCG** is the guide to use for study data submissions to CBER and CDER.
- **TCG** is prepared by an interdisciplinary team from CBER and CDER**.**
- **TCG** is updated, at least, twice a year in March and October.

FDA Webinar Series

- **TCG Webinar Series**
  - Enhances FDA's outreach activities to industry to provide regular updates and clarification on study data standards.
  - Provides FDA with industry feedback through the Webinar Q&A session.
  - Informs FDA on TCG updates, as well as topics for future webinars.

Clinical Outcome Assessments: QS Domain

October 2017 TCG Update

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Outline

1) Legislative background
2) Clinical outcome assessment (COA) introduction
3) Logically skipped items
4) Importance of data from logically skipped items
5) Conclusion

Legislative Background

Legislative Background

- The Prescription Drug User Fee Act (PDUFA) VI was signed on August 18, 2017, and took effect on October 1, 2017
- A key part of PDUFA VI is the enhancement of the incorporation of the patient's voice in drug development and decision making

Legislative Background (cont.)

- The 21st Century Cures Act was signed on December 13, 2016
- Title III of the Act, Subtitle A, is entitled "Patient-Focused Drug Development"

COA Introduction

COA Introduction

- Patient experience data have become more important in the drug development process
- Patient experience data can be captured in a COA

COA Introduction (cont.)

- A COA is 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.

COA Introduction (cont.)

- There are 4 types of COAs
  1) patient-reported outcome (PRO)
  2) clinician-reported outcome (ClinRO)
  3) observer-reported outcome (ObsRO)
  4) performance outcome (PerfO)
- This talk focuses on PROs

COA Introduction (cont.)

- A PRO is a measurement based on a report that comes directly from the patient about the status of the patient's health condition without amendment or interpretation of the patient's response by a clinician or anyone else.

COA Introduction (cont.)

- The outcome can be measured in absolute terms (e.g., severity of a symptom, sign, or state of a disease) or as a change from a previous measure
- PRO measures include
  - rating scales
  - counts of events

COA Introduction (cont.)

- PROs are a key part of patient-focused drug development (PFDD)
- An increasing number of drug submissions have used PROs for efficacy in their primary and secondary endpoints

COA Introduction (cont.)

- Examples of PRO instruments are the Patient Global Impression of Severity (PGIS) and the Short Form-36 (SF-36)

Logically Skipped Items

Logically Skipped Items

- A PRO instrument may have logically skipped items
- This occurs when an instrument item is asked conditionally, based on the response for a previous item in the instrument

Logically Skipped Items (cont.)

- One PRO instrument that has logically skipped items is the Work Productivity and Activity Impairment Questionnaire: General Health V2.0 (WPAI:GH)

Logically Skipped Items (cont.)

1. Are you currently employed (working for pay)? ____NO ____ YES
   If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of your health problems? *Include hours you missed on sick days, times you went in late, left early, etc., because of your health problems. Do not include time you missed to participate in this study.*

   _____HOURS

Logically Skipped Items (cont.)

4. During the past seven days, how many hours did you actually work?

_____HOURS *(If "0", skip to question 6.)*

5. During the past seven days, how much did your health problems affect your productivity while you were working?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If health problems affected your work only a little, choose a low number. Choose a high number if health problems affected your work a great deal.

Consider only how much health problems affected productivity while you were working.

Health problems had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	Health problems completely prevented me from working

CIRCLE A NUMBER

Logically Skipped Items (cont.)

6. During the past seven days, how much did your health problems affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If health problems affected your activities only a little, choose a low number. Choose a high number if health problems affected your activities a great deal.

Consider only how much health problems affected your ability to do your regular daily activities, other than work at a job.

Health problems had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	Health problems completely prevented me from doing my daily activities

CIRCLE A NUMBER

Logically Skipped Items (cont.)

- Another PRO instrument that has logically skipped items is the Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)

Logically Skipped Items (cont.)

- Per the scoring instructions on the National Cancer Institute's website
- Conditional branching should be employed for **electronic** administration of PRO-CTCAE symptom terms that have two or more items

Logically Skipped Items (cont.)

- The logic branches from frequency, then to severity, then to interference
- For example, if frequency is > (greater than) never, you next pose the severity question, and if severity > none, you pose the interference question

Logically Skipped Items (cont.)

17. **PRO-CTCAE™ Symptom Term:** Abdominal pain				
In the last 7 days, how OFTEN did you have PAIN IN THE ABDOMEN (BELLY AREA)?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
In the last 7 days, what was the SEVERITY of your PAIN IN THE ABDOMEN (BELLY AREA) at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
In the last 7 days, how much did PAIN IN THE ABDOMEN (BELLY AREA) INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

Logically Skipped Items (cont.)

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Logically Skipped Items (cont.)

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Logically Skipped Items (cont.)

- Data from questionnaires are included in the QS (questionnaires) SDTM dataset
- Per the CDISC SDTM Implementation Guide v3.2, the QS dataset is in the findings dataset class

Logically Skipped Items (cont.)

- Data from logically skipped instrument items have been inconsistently included in regulatory submissions or not included at all
- There has been a need to create data standards for logically skipped items in PRO instruments
- This data standard was defined in the updated October 2017 TCG V4.0

Logically Skipped Items (cont.)

- Section 4.1.1.3, SDTM Domain Specifications, in the updated TCG says that data from logically skipped items are to be included in QS as follows:

Logically Skipped Items (cont.)

- 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.

Logically Skipped Items (cont.)

- Case #1:
- If instructions on how to record and/or score responses to logically skipped items are available from the instrument developer, then records for logically skipped items should be included in the submission dataset with the following:

Logically Skipped Items (cont.)

- QSSTAT = “NOT DONE”
- QSREASND = “LOGICALLY SKIPPED ITEM”
- QSORRES, QSSTRESC, and QSSTRESN would be assigned according to the instrument’s instructions

Logically Skipped Items (cont.)

- Case #2:
- If instructions on how to record and/or score responses to logically skipped items are **not** available from the instrument developer, then records for logically skipped items should be included in the submission dataset with the following:

Logically Skipped Items (cont.)

- QSSTAT = “NOT DONE”
- QSREASND = “LOGICALLY SKIPPED ITEM”
- QSORRES, QSSTRESC, and QSSTRESN all set to null

Logically Skipped Items (cont.)

- Records from logically skipped instrument items are to be included in SDTM QS to allow for traceability to the source data (i.e., CRF data, eDiary data)
- Data capture mechanisms may need to be modified to allow for the collection of records for logically skipped items

Logically Skipped Items (cont.)

- We strongly recommend that records from logically skipped items in ADaM datasets are carried forward from corresponding records in QS

Logically Skipped Items (cont.)

- From TCG Section 8.3.1:
- “An important component of a regulatory review is an understanding of the provenance of the data (i.e., traceability of the sponsor’s results back to the CRF data)…If the reviewer is unable to trace study data from the data collection of subjects participating in a study to the analysis of the overall study data, then the regulatory review of a submission may be compromised.”

Importance of Data from Logically Skipped Items

Importance of Data from Logically Skipped Items

- Per 21 CFR 314.126, an instrument must be well-defined and reliable : “(b) An adequate and well-controlled study has the following characteristics: … (6) The methods of assessment of subjects’ response are well-defined and reliable”.

Importance of Data from Logically Skipped Items (cont.)

- This includes being able to distinguish between missing values and logically skipped items in an instrument, since a missing value for an item in an instrument is different from the item being logically skipped

Importance of Data from Logically Skipped Items (cont.)

- If that distinction cannot be made, the submitted data are not accurate, and a sponsor is not in compliance with what the FDA requires

Importance of Data from Logically Skipped Items (cont.)

- Thus, it is critical for a **sponsor** to be able to distinguish between logically skipped items in an instrument and items with truly missing values
- Those records should be distinguishable in the submitted QS dataset per the data standards defined in TCG Section 4.1.1.3, as well as in corresponding ADaM datasets

Importance of Data from Logically Skipped Items (cont.)

- Case #1:
- There are numerous methods for handling missing endpoint data in a clinical trial. Those missing data methods can directly impact a clinical trial's efficacy endpoint results, as well as sensitivity analysis results.

Importance of Data from Logically Skipped Items (cont.)

- Case #2:
- Issues can arise if data collected from an instrument have many missing values. Sometimes patients fail to report for visits, fail to complete questionnaires, or withdraw from a clinical trial before its planned completion.

Importance of Data from Logically Skipped Items (cont.)

- Those missing data can introduce bias and interfere with the ability to compare effects in the test group with the control group because only a subset of the initial randomized population contributes. These patient groups may no longer be comparable.

Importance of Data from Logically Skipped Items (cont.)

- Case #3:
- Item-level analyses are conducted during PRO instrument development
- During instrument development, it is necessary to know whether items have truly missing values or are logically skipped

Conclusion

Conclusion

- PROs have become a key part of PFDD
- An increasing number of drug submissions have used PROs for efficacy in their primary and secondary endpoints

Conclusion (cont.)

- Recently passed legislation, as well as FDA regulations, call for patient experience data that are well-defined and reliable
- Those well-defined and reliable data should be included in submissions to the FDA
- The FDA will expect inclusion of records from logically skipped instrument items as a data standard

Thank you

SEND TCG Updates

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Major SEND TCG Updates

- Study Type Section
- SEND Domain Specifications
  - General considerations
  - MI Domain
  - CL Domain
  - PC Domain
- Custom Domains
- Tumor Datasets
- Legacy Data

Section 4.1.3.1 – Study Types

"The Standard for Exchange of Nonclinical Data (SEND) provides the organization, structure, and format of standard nonclinical (animal toxicology studies) tabulation datasets for regulatory submission. The SEND Implementation Guide (SENDIGv3.0) supports single-dose general toxicology, repeat-dose general toxicology, and carcinogenicity studies. SENDIG v3.1 additionally supports respiratory and cardiovascular safety pharmacology studies."

- Addition of SEND 3.1 to the Data Standards Catalog was announced in the Federal Register in August 2017
- Sunset dates for SEND 3.0 were also established
- The SEND 3.1 requirement includes respiratory and cardiovascular safety pharmacology studies

Section 4.1.3.2 – Definitions

"Sponsors should use the VISITDY or --NOMDY variable appropriate to the selected SENDIG version if findings, which were intended to be analyzed together, were collected across multiple study days."

- SENDIG 3.1 uses the --NOMDY variable to group measurements collected on grace days.
  - For SEND 3.0, continue to use VISITDY to indicate grouping
  - For SEND 3.1, use --NOMDY

MI Domain

"When histopathology severity data are collected on a severity scale that cannot be represented using the CDISC MISEV codelist without a loss of scientific accuracy (e.g. data were collected on 3 levels or 4 levels but MISEV specifies 5 levels), severity scores may be represented in MISEV as "1 of 4" "2 of 4" or "1 of 3" as appropriate, where the first number is the score and the second is the number of available severities in the scale. A score of 1 should be the least severe finding. Extend the non-extensible MISEV codelist with the necessary terms to describe the alternative severity scores, include these extended values in the define.xml and nSDRG, and explain any resulting validation error(s) in the nSDRG."

- CDISC provides a 5-level severity scale
  - SLIGHT, MILD, MODERATE, MARKED, SEVERE
- Some organizations have trouble mapping data collected on a 6-level or 4-level scale into the CDISC 5-level scale
- When data are difficult to map, this provides an alternative

MI Example

Study Report

Severity	Control	20 mg/kg
Minimal	1	2
Slight	0	3
Mild	0	5

SEND Problem

Severity	Control	20 mg/kg
MINIMAL	1	2
MILD	0	3
MODERATE	0	5

New TCG Alternative

Severity	Control	20 mg/kg
1 of 6	1	2
2 of 6	0	3
3 of 6	0	5

CL Domain

"The information in CLTEST and CLSTRESC, along with CLLOC and CLSEV when appropriate, should be structured to permit grouping of similar findings and thus support the creation of scientifically interpretable incidence tables. Differences between the representation in CL and the presentation of Clinical Observations in the Study Report which impact traceability to the extent that terms or counts in incidence tables created from CL cannot be easily reconciled to those in the Study Report should be mentioned in the nSDRG."

- Updated to explain that FDA uses the data for incidence tables
- Differences in terms that toxicologists can understand are acceptable (e.g. "seizures" in the Study Report vs. "convulsions observed post dose" in SEND)
- Differences in numbers of animals should be explained (e.g. 12 animals with seizures in the Study Report vs. 15 in SEND)

PC Domain

"If the nominal times are provided in PCELTM, nulls should be avoided for plasma concentrations used to calculate a profile. PCDTC and PCDY variables should be populated with actual/collected information when it available; however, for GLP single dose, repeat dose, or carcinogenicity studies where actual/collected information are documented on paper and not available electronically, these variables may be left null or populated with calculated or nominal dates/times. The use of calculated or nominal dates and times should be mentioned in the nSDRG."

- FDA recognizes that providing exact plasma collection times in PCDTC can be burdensome
- For GLP studies when it is not feasible to provide PCDTC, the column may be:
  - Populated with only the collection date
  - Populated with the collection date and protocol time
  - NULL
- PCDY should still be provided and may be imputed

Custom Domains

"To provide study data that does not fit into an existing SEND domain, draft SEND domain, or published SDTM domain, consider creating a custom dataset aligned with the Study Data Tabulation Model (SDTM). Questions about custom domains should be addressed in pre-submission meetings and documented in the SDSP."

- CDISC provides a CoDEx document that describes which data can be confidently exchanged in SEND
- Sometimes it is necessary to provide additional data to fully represent a study, particularly for nonclinical efficacy studies
- This paragraph provides FDA preferences about how to represent data that are not modeled in the SENDIG

Tumor Datasets

"Carcinogenicity studies should include an electronic dataset of tumor findings to allow for a complete review. At this time sponsors should continue to include the tumor.xpt and associated define.pdf files regardless of whether or not the study is in SEND format (See tumor.xpt file specification and mappings to the SEND standard available in the SENDIG). When both tumor.xpt and SEND are submitted, the sponsor should ensure that data are traceable between tumor.xpt and the SEND datasets. Any information needed to establish traceability should be presented in the nSDRG."

- FDA still requires tumor.xpt
- Discrepancies between SEND datasets, the Study Report, and the tumor.xpt dataset are impossible for reviewers to interpret and thus review cannot be performed
- Ensure that there is consistency across all information submitted for carcinogenicity assessment

Section 8.3.2 – Legacy Data

"For nonclinical studies where data is converted to SEND from a previously established collection system, instances may arise where it is not possible to represent a collected data element as a standardized data element. In these cases, there should be an explanation in the nSDRG as to why certain data elements could not be fully standardized or were otherwise not included in the standardized data submission. As the Study Report should contain a complete representation of the study data in the individual animal listings, no non-standardized electronic study data should be submitted."

- The PDF Study Report should contain all of the collected data in the Individual Animal Listings
- When data elements cannot be provided electronically in SEND, explain in the nSDRG (Nonclinical Study Data Reviewers' Guide)
- No non-standardized study data should be submitted unless requested by a review division

Section 8.3.2 - Legacy Data

"Submission of a Legacy Data Conversion Plan and Report is not expected for nonclinical studies where data were collected in a previously established data collection system."

- Legacy Data Conversion Plans are not expected for nonclinical studies
- Mappings from an established data collection system to SEND are not expected unless requested by a review division

Summary

- The TCG has been updated for SEND 3.1
- Implementation details for MI, CL, and PC
- Custom domains should be discussed pre-submission and documented in the SDSP (Study Data Standardization Plan)
- Ensure consistency among the SEND data, tumor.xpt, and the Study Report in carcinogenicity submissions
- No non-standardized electronic data or Legacy Data Conversion Plans should be included with nonclinical toxicology studies in SEND unless they are requested by a review division

Information For Industry

Click for:

- CFR 21 Part 314
- PDUFA VI
- FDA PRO Guidance for Industry
- BEST (Biomarkers, EndpointS, and other Tools)
- FDA COA Qualification Program
- FDA TCG
- Work Productivity and Activity Impairment Questionnaire: General Health V2.0
- NCI PRO-CTCAE
- PDF of today's slides
- Email any remaining questions to us at: CDERSBIA@fda.hhs.gov

Open Q&A begins shortly – type in your questions now.

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