Submitting Clinical Trial Datasets and Documentation for Clinical Outcome Assessments Using Item Response Theory

Guidance for Industry

Technical Specifications Document

For questions regarding this technical specifications document, contact CDER at cder-edata@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

November 2023
Technical Specifications Document

Revision History

Date	Version	Summary of Revisions
November 2023	1.0	Initial Version

Table of Contents

Contains Nonbinding Recommendations

Submitting Clinical Trial Datasets and Documentation for Clinical Outcome Assessments Using Item Response Theory

Guidance for Industry
Technical Specifications Document[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

1.0 INTRODUCTION

1.1 Purpose

This document provides technical specifications for the submission of clinical outcome assessment (COA) data that use Item Response Theory (IRT) and supplements the FDA Center for Drug Evaluation and Research (CDER) Patient-Focused Drug Development (PFDD) Methodological Guidance Series.[2] As described in the Biomarkers, EndpointS, and other Tools (BEST) Resource glossary,[3] a COA refers to the assessment of a clinical outcome made through a report by a clinician, a patient, a non-clinician observer, or through a performance-based assessment; thus, there are four types of COAs: clinician-reported outcome (ClinRO), patient-reported outcome (PRO), observer-reported outcome (ObsRO), and performance outcome (PerfO) measures.

IRT is a family of mathematical models that describes the functional relationship between item performance, item characteristics, and the patient's status on the construct being measured.[4] COAs that use IRT include static, fixed-form COAs that are developed and/or scored using IRT,

[1]This guidance has been prepared by the Office of Biostatistics in the Center for Drug Evaluation and Research at the Food and Drug Administration. You may submit comments on this guidance at any time. Submit comments to Docket No. FDA-2018-D-1216 (available at https://www.regulations.gov/docket?D=FDA-2018-D-1216) (see the instructions for submitting comments in the docket).

[2]More information is available at FDA's PFDD Guidance web page: https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical.

[3]More information is available at NCBI's web page: https://www.ncbi.nlm.nih.gov/books/NBK338448/def-item/glossary.clinical-outcome-assessment/.

[4]American Educational Research Association, American Psychological Association, National Council on Measurement in Education, 2014, The Standards for Educational and Psychological Testing, Washington (DC): American Educational Research Association Publications.

or COAs that are administered using IRT-based Computerized Adaptive Testing (CAT). CAT is a sequential form of individual testing administered by a computer in which successive items in the COA measure are selected for administration based primarily on the item's psychometric properties and content in relation to the patient's responses to previous items[5]. COAs that use IRT can leverage an item bank for item selection. An item bank represents the total set of items from which a subset is selected during COA measure development or selected for the patient during adaptive testing.[6]

1.2 Scope

COAs covered in this guidance (referred to as '*covered COAs*' throughout this document) include (1) fixed-form (i.e., static, fixed-length) COAs that are developed and/or scored using IRT and (2) COAs administered using IRT-based CAT. This document provides specifications for the submission of Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) datasets. These technical specifications aim to provide general guidelines for standardized dataset content and structure, along with supporting documentation, to facilitate FDA review of the covered COA within the marketing application that the submitted data are intended to support. The SDTM and ADaM specifications outlined in section 4.0 Overview of Dataset Specifications are not prescriptive and do not include an exhaustive list of all datasets, variables, and controlled terminologies to be submitted for FDA review.

These technical specifications provide an opportunity for dialogue between the sponsor and the Agency on issues related to trial design or conduct that may affect the content of these datasets. The specifications outlined in section 3.0 Documentation Specifications and section 4.0 Overview of Dataset Specifications are pursuant to discussions with FDA and may vary by clinical drug development program and clinical trial therein. Agreement on the covered COA measure(s) used to collect trial data and analyses of the resulting COA data should be discussed with FDA as early as possible in a medical product development program; for example, prior to trial initiation. Sponsors are strongly encouraged to use the resources described in section 1.3 Relationships to Other Documents and to seek Agency input for confirmation and clarification as needed.

1.3 Relationship to Other Documents

These technical specifications have been drafted in accordance with the business rules and assumptions outlined in the CDISC SDTM,[7] the SDTM Implementation Guide[8], the ADaM[9], and the ADaM Implementation Guide (ADaMIG). As new versions of the models and implementation guides become available, these technical specifications may be updated accordingly to maintain alignment. In addition, the FDA Study Data Technical Conformance

[5]American Educational Research Association, American Psychological Association, National Council on Measurement in Education, 2014, The Standards for Educational and Psychological Testing, Washington (DC): American Educational Research Association Publications.
[6]Ibid.
[7]More information is available at CDISC's SDTM web page: https://cdisc.org/standards/foundational/sdtm.
[8]More information is available at CDISC's SDTMIG web page: https://cdisc.org/standards/foundational/sdtmig.
[9]More information is available at CDISC's ADaM web page: https://cdisc.org/standards/foundational/adam.

Guide (sdTCG)[10] provides general specifications and recommendations for submitting datasets using the SDTM and ADaM standards. Sponsors should review the FDA Data Standards Catalog[11] to ensure data submissions follow FDA-supported standards.

In addition, sponsors should reference the following:

- FDA PFDD Guidance series[12]
- CDISC Controlled Terminology[13]
- CDISC Questionnaires, Ratings and Scales (QRS) Supplements and CDISC QRS Resources, which includes QRS Naming and Business Rules[14]

2.0 RELEVANT ACRONYMS

Abbreviation	Description
ADaM	Analysis Data Model
ADaMIG	Analysis Data Model Implementation Guide
ADRG	Analysis Data Reviewer's Guide
BEST	Biomarkers, EndpointS, and other Tools
BDS	Basic Data Structure
CAT	Computerized Adaptive Testing
CDISC	Clinical Data Interchange Standards Consortium
CDER	Center for Drug Evaluation and Research
ClinRO	Clinician-Reported Outcome
COA	Clinical Outcome Assessment
CRF	Case Report Form
cSDRG	Clinical Study Data Reviewer's Guide
CSR	Clinical Study Report
DDT	Drug Development Tool
FDA	Food and Drug Administration
IND	Investigational New Drug
IRT	Item Response Theory
NCBI	National Center for Biotechnology Information
NCI EVS	National Cancer Institute Enterprise Vocabulary Services
ObsRO	Observer-Reported Outcome
PerfO	Performance Outcome
PFDD	Patient-Focused Drug Development

[10]More information is available at FDA's Study Data Standards Resources web page: https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources.
[11]Ibid.
[12]More information is available at FDA's PFDD Guidance series web page: https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical.
[13]More information is available at NCI's web page: https://datascience.cancer.gov/resources/cancer-vocabulary/cdisc-terminology.
[14]More information is available at CDISC's QRS web page: https://cdisc.org/standards/foundational/qrs.

PRO	Patient-Reported Outcome
QRS	Questionnaires, Ratings and Scales
SAP	Statistical Analysis Plan
sdTCG	Study Data Technical Conformance Guide
SDTM	Study Data Tabulation Model
SDTMIG	Study Data Tabulation Model Implementation Guide
SDTMIG-MD	Study Data Tabulation Model Implementation Guide for Medical Devices

3.0 DOCUMENTATION SPECIFICATIONS

This section details the content and timing of documentation to be submitted for covered COAs. Note the IRT terminology referenced within the submission should be explicitly defined in the study protocol and used consistently throughout the submission.

3.1 Contents of Covered COA Documentation

For a covered COA, the recommended documentation to be submitted to FDA is the following:

- COA name, version, and copyright information (if applicable)
- A copy of the measure with all items and response options for covered COAs that are administered as static, fixed-form. For covered COAs administered using CAT, a screenshot of each item in the item bank should be submitted
- The item dataset described in section 4.1.1 Item Dataset
- The COA measure instructions received by the reporter (e.g., patient, clinician, caregiver)
- The user manual, including training materials and instructions for administration and scoring
- Operational details (e.g., acceptable screen sizes, operating systems, and other specifications, as well as types of assistance provided, if applicable)
- The handling and mitigation of server, power, and/or internet outage issues
- Supporting software datasets and code
- A detailed description of the calibration sample (i.e., the sample of respondents used to estimate the item parameters)
- For covered COAs where IRT is used for scoring the following additional information should be submitted to FDA:
    - Scoring details, including methods for generating scores (e.g., latent factor score (referred to as theta score throughout this document), scaled score)

- Conversion table(s) used to convert a theta score to other transformed scores (e.g., T-score), if applicable

- Psychometric software (e.g., the software name and version)

For covered COAs administered using CAT, it is recommended that the following documentation be submitted to FDA in addition to the documentation listed above:

- Details of item selection or routing algorithm (e.g., the algorithm used to select the next item or sets of items for the patient with content constraints and/or item exposure control (if applicable))

- The starting criteria with justification

- The termination criteria (i.e., the stopping rule) with justification

Additional documentation can be requested to facilitate the Agency's review of the IRT analyses results. It is recommended that the sponsor consult with the review division to discuss the submission of documentation.

3.2 Timing of Covered COA Documentation

It is strongly recommended that the sponsor consult the Agency early during the IND phase to (1) determine the appropriate level of evidence to submit for the covered COA and (2) obtain agreement on the proposed fixed/static COA measure and/or item bank *prior* to the sponsor conducting the registration trial(s) (i.e., the trial(s) intended to contribute to substantial evidence of effectiveness). It is recommended that the agreed-upon COA evidence, including the item dataset described in section 4.1.1 Item Dataset, be submitted to FDA during the IND phase. If submission is not possible during the IND phase, the sponsor should consult with the review division.

4.0 OVERVIEW OF DATASET SPECIFICATIONS

Dataset specifications detail the CDISC datasets that are used to support covered COA data tabulation and analyses. Sponsors should implement the CDISC SDTM standard when submitting clinical tabulation data and the CDISC ADaM standard when submitting analysis data. This section supplements existing guidance by providing specifications for submitting covered COA data but does not encompass all data to be submitted for a clinical trial. As documented in the FDA sdTCG,[15] SDTM and ADaM datasets should be accompanied by informative metadata provided in a compliant data definition file (i.e., Define-XML) and are expected to be accompanied by a Clinical Study Data Reviewer's Guide (cSDRG) and an Analysis Data Reviewer's Guide (ADRG), respectively. Standard CDISC Controlled

[15]More information is available at FDA's Study Data Standards Resources web page: https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources.

Terminology[16] developed and maintained by CDISC and National Cancer Institute Enterprise Vocabulary Services (NCI EVS) should be used where applicable. Sponsor extensions to extensible codelists and use of alternate (e.g., non-CDISC or sponsor-defined) terminologies should be indicated in the study metadata (e.g., Define-XML file, cSDRG, and other supportive documentation). In addition, software programs used to create ADaM datasets and analyze covered COA data should be submitted with the marketing application for FDA review.

4.1 SDTM Specifications

This section details the SDTM specifications for (1) the item dataset, (2) the Questionnaires (QS) dataset, and (3) the Trial Summary (TS) dataset.

4.1.1 Item Dataset

Sponsors should create and submit an item dataset (referred to as the ZQ dataset throughout this document) that provides all items, response options, and associated model parameters for a covered COA. The ZQ dataset does not contain individual patient data. When an item bank is used either during measure development or during measure administration, the ZQ dataset should contain information for all items within the item bank. When an item bank is not used, such as when IRT is only used in scoring, the ZQ dataset should contain information for all items within the fixed/static COA. Examples of ZQ dataset parameters (referenced as ZQPARM in Table 1) may include, but are not limited to, the following:

- All possible numeric and/or character response values for items with categorical responses
- Minimum and maximum numeric values for items using continuous scales by design
- Character interpretation of minimum and maximum values for items using continuous scales by design
- Item loading parameters, or equivalent, for items based on continuous response options
- Item location and/or threshold parameters for items based on dichotomous or polytomous response options
- Item intercept for an item using a count response scale
- Item slope(s) (i.e., item discrimination parameter(s)) for each item

The list of variables for the recommended item dataset is provided in Table 1, and an example ZQ dataset is provided in Appendix 5.1. Additional qualifiers such as units or subcategory (i.e., ZQSCAT) may be added if relevant for the covered COA.

[16]More information is available at NCI's web page: https://datascience.cancer.gov/resources/cancer-vocabulary/cdisc-terminology.

Table 1. Specifications for Item Variables

Variable Name	Variable Label	Type	Comments
STUDYID	Study Identifier	Char	This is the Unique Identifier for a study.
DOMAIN	Domain	Char	This is a two-character abbreviation for the domain (e.g., ZQ).
RDOMAIN	Related QRS Domain Abbreviation	Char	This is the related QRS domain in which the covered COA data resides within a study (e.g., FT, QS, RS).
ZQSEQ	Sequence Number	Num	This is the sequence number assigned to ensure uniqueness of records within the ZQ dataset.
ZQCAT	Category of Item	Char	The measure name(s) and version number(s) should be provided within ZQCAT. Controlled Terminology for FTCAT, QSCAT, or RSCAT should be implemented in ZQCAT if applicable; if not, ZQCAT should be constructed according to CDISC QRS Naming and Business Rules. The most common name that the measure is known by should be used; this could either be the complete name of the measure or an acronym.
ZQTESTCD	Item --TESTCD	Char	A topic variable for ZQ and a short name for the item name in ZQTEST. Controlled Terminology should be implemented if applicable; if not, construct these according to CDISC QRS Naming and Business Rules.
ZQTEST	Item --TEST name	Char	This is the long name of the item. SDTM Controlled Terminology should be implemented if applicable; if not, construct these according to CDISC QRS Naming and Business Rules.
ZQPARMCD	Item Parameter Short Name	Char	This is the short name for the Item Parameter. Naming conventions for ZQPARMCD should make it easy to discern if related parameters are grouped together (e.g., if multiple point estimates are present for threshold parameters as illustrated in Appendix 5.1).
ZQPARM	Item Parameter	Char	This is the long name for the Item Parameter.
ZQVALN	Numeric Parameter Value	Num	The numeric value corresponds to the parameter identified by ZQPARMCD and ZQPARM. The sponsor should consider the appropriate number of decimal places to be provided within ZQVALN given the parameter.
ZQVALC	Character Parameter Value	Char	The character value corresponds to the parameter identified by ZQPARMCD and ZQPARM.
ZQSE	Standard Error	Num	This is the standard error for an estimated Numeric Parameter Value (ZQVALN). For example, ZQSE is provided when ZQVALN represents an estimated threshold parameter or item slope. Item slope may be estimated based on the IRT model implemented.

4.1.2 Questionnaires Dataset

Covered COA data are typically represented in the SDTM Questionnaires (QS) dataset, the Functional Tests (FT) dataset, or the Disease Response and Clin Classification (RS) dataset. The dataset should be created using the assumptions and business rules provided within the SDTMIG and the FDA sdTCG. For brevity, the tabulation dataset containing covered COA data for individual patients is referenced as the QS dataset throughout the remainder of this document, though it is understood that other datasets may contain covered COA data (e.g., FT, RS). For select measures, CDISC publishes QRS Supplements[17] that provide guidance on representing named COA measures in the SDTM. CDISC also provides submission values within the Controlled Terminology[18] related to named COA measures. These resources should be consulted for guidance on a covered COA measure, in addition to the guidance provided in the SDTM and SDTMIG.

4.1.2.1 General Considerations

The QS dataset represents the covered COA data as collected for individual patients at distinct assessment timepoints. The subset of standard QS variables in Table 2 is included here to clarify how they should be completed for covered COA measures to foster consistency and standardization across industry. An example QS dataset is provided in Appendix 5.2.

Table 2. Specifications for a Subset of QS Variables

Variable Name	Variable Label	Type	Comments
QSCAT	Category of Question	Char	The measure name and version number should be provided within QSCAT. Controlled Terminology should be implemented if applicable; if not, QSCAT should be constructed according to CDISC QRS Naming and Business Rules. The most common name that the measure is known by should be used, which can either be the complete name of the measure or an acronym.
QSTESTCD	Question Short Name	Char	A topic variable for QS and short name for the value in QSTEST. Controlled Terminology should be implemented if applicable; if not, construct the name according to CDISC QRS Naming and Business Rules. QSTESTCD should begin with a short code for the measure followed by the item number (e.g., ABC01). In cases where item numbers are absent, sequential numbers starting with 01 should be used, and can be shortened to 1 to accommodate the eight-character limit for values of QSTESTCD. The value in QSTESTCD

[17]More information is available at CDISC's QRS web page: https://cdisc.org/standards/foundational/qrs.
[18]More information is available at NCI's web page: https://datascience.cancer.gov/resources/cancer-vocabulary/cdisc-terminology.

Variable Name	Variable Label	Type	Comments
			should correspond to the value in ZQTESTCD to support traceability. See the example in Appendix 5.2.
QSTEST	Question Name	Char	This is the name of the item or, if applicable, the *source data summary score*[19] used to obtain the measurement or finding. QSTEST should start with a short code for the measure followed by a hyphen and a brief description. Controlled Terminology should be implemented if applicable; if not, construct according to CDISC QRS Naming and Business Rules. If QSTEST is > 40 characters in length, put meaningful text in QSTEST and describe the full-text in the study metadata (e.g., the annotated Case Report Form (CRF), the cSDRG, or the Define-XML). For each patient and assessment timepoint where the covered COA measure is planned to be administered per the protocol-defined schedule of assessments, a record should be provided for each item or source data summary score within the measure (See section 4.1.2.2 Handling of Missing Data and section 4.1.2.3 Handling of Data Not Collected due to Skip Logic or Computerized Adaptive Testing).
QSREFID	Reference Identifier	Char	Sequential ordering of all items the patient was administered regardless of whether a response was provided. Recommended for covered COA measures that use CAT, since item selection and/or the order of item administration from the item bank can vary by patient and/or by assessment timepoint.
QSSTAT	Completion Status	Char	This is populated as 'NOT DONE' when an item score (response) or source data summary score is empty/null. QSSTAT is empty/null if a result exists in QSORRES.
QSREASND	Reason Not Performed	Char	This is used in conjunction with QSSTAT when QSSTAT = 'NOT DONE' to describe why an item score or source data summary score is empty/null (See section 4.1.2.2 Handling of Missing Data and section 4.1.2.3 Handling of Data Not Collected due to Skip Logic or Computerized Adaptive Testing).

The following are additional considerations:

Additional content captured by the source should be submitted either as additional rows with relevant QSTEST and QSTESTCD values within the QS dataset or within a Supplemental

[19] S*ource data summary scores* are summary scores (e.g., total scores) that are source data (e.g., data reported within a CRF) and are submitted in the QS dataset.

Questionnaires (SUPPQS) dataset. Additional content is dependent on the covered COA measure administered, and if needed for analysis, should be copied into the applicable ADaM dataset. Example content captured within SUPPQS for each patient and assessment timepoint include the following:

- **Data Collection Mode:** The mode of data collection used in the administration of the covered COA measure, if differing from the protocol and/or varying across patients, assessment timepoints, or sites (e.g., clinical trial site, home). Examples of data collection mode may include paper-based administration, handheld electronic device, computer web-based application, or telephone-based administration.

- **Data Collector:** In cases where a PRO measure is not self-administered (i.e., not independently completed by the patient without any assistance), the individual administering the PRO measure to the patient (e.g., caregiver, study staff member) by reading items to the patient and/or recording the patient's responses.

- **Language:** The language in which the measure was administered to the patient.

- **Response Time:** The time taken to respond to each item administered within a covered COA measure and/or the time taken to respond to the total measure (used for assessing quality control).

4.1.2.2 Handling of Missing Data

Understanding the reasons for and prevalence of missing covered COA data are critical to support FDA review and regulatory decision-making. Missing data should be represented within the QS dataset with the reason for missingness captured under 'Reason Not Performed' (QSREASND). The handling of missing data may differ depending on whether the covered COA is fixed/static or is administered using CAT. Item responses may be missing for one item, a subset of items, or all items within a covered COA, and Table 3 provides scenario-specific recommendations for displaying covered COA data that are missing at a planned (i.e., per protocol) assessment timepoint. Appendix 5.2 demonstrates scenarios for representing missing data within the QS dataset. CDISC QRS Supplements[20] provide additional guidance on modeling missing data for named COA measures in SDTM datasets, including the modeling of timing variables.

[20]More information is available at CDISC's QRS web page: https://cdisc.org/standards/foundational/qrs.

Table 3. Recommended QS Representation of Missing Data

Scenario	Recommended Representation in QS Dataset
The patient did not respond to an item administered within a covered COA.	The row for the missing item response should include: • QSSTAT = 'NOT DONE' • 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: • QSSTAT = 'NOT DONE' • QSREASND is populated if known/collected (e.g., QSREASND = 'NOT CALCULABLE'). Otherwise, QSREASND is empty/null.
For a fixed/static covered COA measure, the patient was not administered the measure at a planned (per protocol) assessment timepoint.	The row for each missing item response and source data summary score within the measure should include: • QSSTAT = 'NOT DONE' • 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 measure due to adverse event, patient refusal, patient did not provide measure, unable to contact, study site failed to administer or other site staff error, technological problems with a measure administered electronically, or patient was unable to attend a scheduled study visit due to hospitalization.
For a covered COA measure administered using CAT, the patient was not administered the measure for a planned (per protocol) assessment timepoint.	Given the exact items to be administered during CAT are unknown, individual rows cannot be provided for each missing item. It is recommended that a row for each item within the item bank not be submitted; rather, a single row indicating the COA measure was not administered should be provided and include: • QSTESTCD = 'QSALL' • QSTEST = 'All Questions' • QSSTAT = 'NOT DONE' • QSREASND contains the reason the patient was not administered the COA measure, if known/collected.

4.1.2.3 *Handling of Data Not Collected due to Use of Skip Logic or Computerized Adaptive Testing*

Separate from missing data, covered COA data may not be collected from the patient due to the use of CAT or skip logic to administer COA items. When the patient is not administered all items from an item bank due to the use of CAT, a row for each remaining unadministered item within the item bank should not be included within the QS dataset. Rather, only the administered items for CAT-administered measures should be submitted within the QS dataset as illustrated in Appendix 5.1. Conversely, when implemented, skip logic may be created based on the response

to certain items. When the patient is not administered an item within a covered COA measure due to the use of skip logic, the representation in the QS dataset should follow the guidance provided in the sdTCG.

4.1.3 Trial Summary Dataset

Data related to the trial summary should be stored in the TS dataset. Of particular interest to FDA is the frequency with which these technical specifications are used to create and submit trial data. Per the FDA sdTCG, sponsors may include the following parameters and associated values in the TS dataset to indicate that these technical specifications were used for the study:

- TSPARAMCD = 'FDATCHSP'
- TSPARAM = 'FDA Tech Spec'
- TSVAL = 'IRT-Based COAs Technical Specifications Guidance v1.0'

4.2 ADaM Specifications

This section provides specifications for the ADaM dataset containing analysis-ready covered COA data (referenced in this document as the 'ADQS' dataset), which are derived from covered COA data in the SDTM QS dataset discussed in section 4.1.2 SDTM Dataset Containing Covered COA Data in conjunction with other SDTM and ADaM data.

4.2.1 General Considerations

The ADQS dataset described in this section follows the ADaM Basic Data Structure (BDS). In addition to variables for treatment assignment, stratification, subgrouping, and other covariates needed for analysis, the ADQS dataset should contain all individual items and summary scores (e.g., raw score, theta score, scale score (e.g., a standardized score such as T-score)) and associated standard errors.

For CAT, additional information such as the number of items that were scored (i.e., scored count) and the number of items to which the patient responded (i.e., total item count) should be submitted to validate that the termination criteria for the CAT was met and that theta score was not calculated prematurely. Table 4 contains specifications for a subset of standard ADQS variables to clarify how they should be completed for covered COA measures to foster consistency and standardization across industry as well as traceability. Table 4 does not include all ADQS variables to be submitted, such as timing and treatment variables. An example ADQS dataset is provided in Appendix 5.3.

Table 4. Specifications for a Subset of ADQS Variables

Variable Name	Variable Label	Type	Comments
PARCAT1	Parameter Category 1	Char	The measure name(s) and version(s) should be provided within PARCAT1 for each item, summary score, or associated scoring parameter provided in PARAM to differentiate between measures administered during the study. The measure name may match the value stored in the variable QS.QSCAT from the input SDTM QS dataset.
PARAM	Parameter	Char	The description of the analysis parameter, including individual items, summary scores (e.g., raw score, theta score, scale score (e.g., a standardized score such as T-score)), and associated standard errors. The value of PARAM may match the value stored in QS.QSTEST for parameters existing in the input SDTM QS dataset. Individual parameters are needed for each summary score. Documentation for derived parameters should be provided in submitted study metadata (e.g., the Define-XML file and the ADRG).
PARAMCD	Parameter Code	Char	The short name of the analysis parameter in PARAM. The value of PARAMCD may match the values stored in QS.QSTESTCD for parameters existing in the input SDTM QS dataset.
AVAL / AVALC	Analysis Value / Analysis Value (C)	Num / Char	The analysis value for each parameter described by PARAM. For parameters existing in the input SDTM QS dataset, quantitative values used for analysis and captured in AVAL may be copied from QS.QSSTRESN, and qualitative values used for analysis and captured in AVALC may be copied from QS.QSSTRESC. In some cases, it is acceptable to populate AVAL for qualitative values. Reference the ADaMIG for details around populating AVAL and AVALC. Study metadata should describe how AVAL and AVALC are calculated for derived parameters.
DTYPE	Derivation Type	Char	Analysis value derivation method. DTYPE should be populated with the algorithm or statistical method used when AVAL or AVALC has been imputed or derived differently than the other analysis values within the parameter. Reference the ADaMIG for details around the submission of DTYPE. This document utilizes phantom records (i.e., where DTYPE = 'PHANTOM') to represent missing item scores or summary scores (See section 4.2.2 Handling of Missing Data and the examples within Appendix 5.3). Based on the study attributes, alternate DTYPE values may be used to handle missing data depending on the imputation method(s) implemented. When imputation is performed, imputation rules are included in the study's Statistical Analysis Plan (SAP). Imputation methods are not specified within this document for covered COAs.
Variables in ADQS copied from input SDTM QS Dataset			
QSSEQ	Sequence Number	Num	

Variable Name	Variable Label	Type	Comments
VISIT	Visit	Char	Sponsors should include any SDTM variables in the ADQS dataset needed to provide traceability to the source SDTM QS dataset.
VISITNUM	Visit Number	Num	
QSSTAT	Completion Status	Char	Sponsors should include SDTM variables that provide explanations for missing item scores and missing source data summary scores. See Comments for QSSTAT and QSREASND provided in Table 2. Specifications for a Subset of QS Variables.
QSREASND	Reason Not Performed	Char	

4.2.2 Handling of Missing Data

As discussed in SDTM section 4.1.2.2 Handling of Missing Data and section 4.1.2.3 Handling of Data Not Collected due to Skip Logic or Computerized Adaptive Testing, understanding the reasons for and prevalence of missing COA data or COA data not collected are critical to support FDA review and regulatory decision-making. Approaches to represent missing covered COA data within the ADQS dataset include:

- Copying records from the SDTM QS dataset, where QS.QSSTAT = 'NOT DONE' and QS.QSREASND is populated with the reason the item(s) and/or summary score(s) are missing, or

- Deriving phantom records in the ADQS dataset (e.g., where DTYPE = 'PHANTOM').

When QS.QSREASND is populated within the SDTM QS dataset for a record, the value should be copied into the ADQS dataset within QSREASND. Phantom records should only be derived in the ADQS dataset when rows for the missing data do not exist in the SDTM QS dataset. For these records, phantom records should be derived for scenarios shown in Table 3: Recommended QS Representation of Missing Data. For example, if a patient was not administered a CAT measure due to skipping a visit and a row for the measure is not provided in the SDTM QS dataset, phantom records should be derived in the ADaM ADQS dataset for the measure. Deriving phantom records is one solution to represent missing data; however, based on the study attributes, values may be imputed instead. When applicable, if QS.QSREASND is not populated, a sponsor-defined analysis variable for Reason Not Performed (e.g., ADQS.AREASND) may be useful to indicate the reason (if known) that an item or measure was not completed, such as for phantom records. The example provided in Appendix 5.3 illustrates the representation of missing data.

5.0 APPENDIX

5.1 Example Item Dataset

Table A1 shows an example of the Study Data Tabulation Model (SDTM) item dataset that is recommended to be submitted for covered clinical outcome assessments (COAs). The parameters and their associated values are provided for illustrative purposes only; all parameters relevant to support the review should be submitted.

Table A1, shown in two parts, illustrates the tabulation of one item containing polytomous response options from the item bank, which corresponds to a single ZQTEST value (i.e., Item 1):

- Rows 1-5 represent the five discrete response options where ZQVALN represents the Numeric Parameter Value and ZQVALC represents the Character Parameter Value for Item 1. Both the numeric and character values should be submitted when applicable. When discrete response options are present for a given parameter, all possible response options should be submitted within ZQVALN and/or ZQVALC as shown in Table A1.

- Rows 6-10 represent the discrete threshold parameters and item slope for the polytomous response options. Standard Error (ZQSE) is provided for each estimated threshold parameter. ZQSE should be provided when values are estimated, and Item Parameter (ZQPARM) values will differ based on the Item Response Theory (IRT) model used.

Table A1. (Part 1) Subset of Sample ZQ

Row	STUDYID	DOMAIN	RDOMAIN	ZQSEQ	ZQCAT	ZQTEST	ZQTESTCD
1	StudyA	ZQ	QS	1	Example Item Bank v.1.0	EIB01-Item 1	EIB01
2	StudyA	ZQ	QS	2	Example Item Bank v.1.0	EIB01-Item 1	EIB01
3	StudyA	ZQ	QS	3	Example Item Bank v.1.0	EIB01-Item 1	EIB01
4	StudyA	ZQ	QS	4	Example Item Bank v.1.0	EIB01-Item 1	EIB01
5	StudyA	ZQ	QS	5	Example Item Bank v.1.0	EIB01-Item 1	EIB01
6	StudyA	ZQ	QS	6	Example Item Bank v.1.0	EIB01-Item 1	EIB01
7	StudyA	ZQ	QS	7	Example Item Bank v.1.0	EIB01-Item 1	EIB01
8	StudyA	ZQ	QS	8	Example Item Bank v.1.0	EIB01-Item 1	EIB01
9	StudyA	ZQ	QS	9	Example Item Bank v.1.0	EIB01-Item 1	EIB01
10	StudyA	ZQ	QS	10	Example Item Bank v.1.0	EIB01-Item 1	EIB01

Table A1. (Part 2) Subset of Sample ZQ

Row	ZQPARMCD	ZQPARM	ZQVALN	ZQVALC	ZQSE
1	RESP	Item Response	1	Never	
2	RESP	Item Response	2	Rarely	
3	RESP	Item Response	3	Sometimes	
4	RESP	Item Response	4	Often	
5	RESP	Item Response	5	Always	
6	TPAR	Threshold Parameter	-1.2		0.29
7	TPAR	Threshold Parameter	-0.6		0.14
8	TPAR	Threshold Parameter	0.1		0.02
9	TPAR	Threshold Parameter	0.8		0.13
10	SLOPE	Item Slope	2.0		0.22

5.2 Example SDTM Questionnaires Dataset

Table A2 shows an example of tabulated item response scores using the Questionnaires (QS) domain specifications for a single patient who was administered a COA measure via CAT across three on-site assessment timepoints as specified by the protocol (not displayed), where the item bank (not displayed) contains eight questions. Where the measure was not completed as expected, Table A2 illustrates how missing data are submitted in the QS dataset for a subset of variables. Values within Numeric Finding in Standard Units (QSSTRESN) and Reason Not Performed (QSREASND) are provided for illustrative purposes; submitted values should be relevant in the context of the study. Scenarios displayed in Table A2, shown in two parts, include:

- Rows 1-5 and rows 7-9 present the administered items during Visit 1 and Visit 3, respectively. Due to adaptive testing, the patient was administered items 1, 3, 4, 5, and 7 from the item bank during Visit 1. Thus, unadministered items 2, 6, and 8 are excluded from the QS dataset. During Visit 3, the patient was administered items 1, 5, and 8 from the item bank. Thus, unadministered items 2, 3, 4, 6, and 7 are excluded.

    - Reference Identifier (QSREFID) is populated for all administered items in the QS dataset in chronological order, even if the patient did not provide a response to an item.

- Row 2 presents the scenario where the patient did not provide a response to an administered item. Within CAT, this may occur when the measure allows a patient to skip an administered item by selecting the 'Next' button to continue without selecting a response for the item.

    - Completion Status (QSSTAT) = 'NOT DONE' and QSREASND is populated with the reason when a patient did not provide a response to an item if known/collected (e.g., 'RESPONSE NOT PROVIDED').

    - QSORRES, QSSTRESC, and QSSTRESN are empty/null.

- Row 6 presents the scenario where the covered COA was not administered during Visit 2 due to a study site error. This scenario should be displayed as a single record in the QS dataset with the following:

    - QSTEST = 'All Questions' and QSTESTCD = 'QSALL'.

    - QSREFID, QSORRES, QSSTRESC, and QSSTRESN are empty/null.

    - QSSTAT = 'NOT DONE' and QSREASND is populated with the reason the COA measure was not administered if known/collected (e.g., 'STUDY SITE FAILED TO ADMINISTER').

Table A2. (Part 1) Subset of Sample QS

Row	USUBJID	VISIT	QSSEQ	QSCAT	QSTEST	QSTESTCD
1	A_100_1001	VISIT 1	1	Example Item Bank v.1.0	EIB01-Item 1	EIB01
2	A_100_1001	VISIT 1	2	Example Item Bank v.1.0	EIB03-Item 3	EIB03
3	A_100_1001	VISIT 1	3	Example Item Bank v.1.0	EIB04-Item 4	EIB04
4	A_100_1001	VISIT 1	4	Example Item Bank v.1.0	EIB05-Item 5	EIB05
5	A_100_1001	VISIT 1	5	Example Item Bank v.1.0	EIB07-Item 7	EIB07
6	A_100_1001	VISIT 2	6	Example Item Bank v.1.0	All Questions	QSALL
7	A_100_1001	VISIT 3	7	Example Item Bank v.1.0	EIB01-Item 1	EIB01
8	A_100_1001	VISIT 3	8	Example Item Bank v.1.0	EIB05-Item 5	EIB05
9	A_100_1001	VISIT 3	9	Example Item Bank v.1.0	EIB08-Item 8	EIB08

Table A2. (Part 2) Subset of Sample QS

Row	QSREFID	QSORRES	QSSTRESC	QSSTRESN	QSSTAT	QSREASND
1	1	Often	Often	4		
2	2				NOT DONE	RESPONSE NOT PROVIDED
3	3	Often	Often	4		
4	4	Always	Always	5		
5	5	Sometimes	Sometimes	3		
6					NOT DONE	STUDY SITE FAILED TO ADMINISTER
7	1	Rarely	Rarely	2		
8	2	Never	Never	1		
9	3	Never	Never	1		

5.3 Example ADaM Questionnaires Analysis Dataset

Table A3 shows an example ADQS dataset for the same patient and scenario descriptions as those provided in Appendix 5.2. Note that this table only shows a subset of variables to be submitted in the ADQS dataset; additional variables, such as population flags and treatment variables, are not provided as these depend on individual study needs. In this example, outputs of a psychometric software, including summary scores (e.g., raw score, theta score, T-score) and their associated standard errors, are derived in the ADQS dataset for each assessment timepoint. Values within Analysis Value (AVAL) are provided for illustrative purposes only. Scenarios displayed in Table A3, shown in two parts, include:

- Rows 1-9 and 15-21 present records for Visits 1 and 3, respectively, where Visit 1 represents the baseline visit:
    - Rows 1-5 and rows 15-17 present the administered items, copied from the SDTM QS dataset.
    - Rows 6-9 and rows 18-21 present the summary scores and standard errors derived in the ADQS dataset.
- Rows 10-14 present records for Visit 2:
    - Row 10 presents the single record copied from the SDTM QS dataset where QSTESTCD = ‘QSALL’, provided for traceability.

- Rows 11-14 present phantom records for each summary score and standard error derived in the ADQS dataset. For each row:
  - DTYPE = 'PHANTOM'.
  - AVAL is empty/null.

Table A3. (Part 1) Subset of Sample ADQS

Row	USUBJID	AVISIT	PARCAT1	PARAM	PARAMCD
1	A_100_1001	BASELINE	Example Item Bank v.1.0	EIB01-Item 1	EIB01
2	A_100_1001	BASELINE	Example Item Bank v.1.0	EIB03-Item 3	EIB03
3	A_100_1001	BASELINE	Example Item Bank v.1.0	EIB04-Item 4	EIB04
4	A_100_1001	BASELINE	Example Item Bank v.1.0	EIB05-Item 5	EIB05
5	A_100_1001	BASELINE	Example Item Bank v.1.0	EIB07-Item 7	EIB07
6	A_100_1001	BASELINE	Example Item Bank v.1.0	EIB-Raw Score	EIBRAW
7	A_100_1001	BASELINE	Example Item Bank v.1.0	EIB-Theta Score	EIBTHETA
8	A_100_1001	BASELINE	Example Item Bank v.1.0	EIB-T-Score	EIBTSCR
9	A_100_1001	BASELINE	Example Item Bank v.1.0	EIB-Standard Error	EIBSE
10	A_100_1001	VISIT 2	Example Item Bank v.1.0	All Questions	QSALL
11	A_100_1001	VISIT 2	Example Item Bank v.1.0	EIB-Raw Score	EIBRAW
12	A_100_1001	VISIT 2	Example Item Bank v.1.0	EIB-Theta Score	EIBTHETA
13	A_100_1001	VISIT 2	Example Item Bank v.1.0	EIB-T-Score	EIBTSCR
14	A_100_1001	VISIT 2	Example Item Bank v.1.0	EIB-Standard Error	EIBSE
15	A_100_1001	VISIT 3	Example Item Bank v.1.0	EIB01-Item 1	EIB01
16	A_100_1001	VISIT 3	Example Item Bank v.1.0	EIB05-Item 5	EIB05
17	A_100_1001	VISIT 3	Example Item Bank v.1.0	EIB08-Item 8	EIB08
18	A_100_1001	VISIT 3	Example Item Bank v.1.0	EIB-Raw Score	EIBRAW
19	A_100_1001	VISIT 3	Example Item Bank v.1.0	EIB-Theta Score	EIBTHETA
20	A_100_1001	VISIT 3	Example Item Bank v.1.0	EIB-T-Score	EIBTSCR
21	A_100_1001	VISIT 3	Example Item Bank v.1.0	EIB-Standard Error	EIBSE

Table A3. (Part 2) Subset of Sample ADQS

Row	AVAL	QSSEQ	VISIT	DTYPE	QSSTAT	QSREASND
1	4	1	VISIT 1			
2		2	VISIT 1		NOT DONE	RESPONSE NOT PROVIDED
3	4	3	VISIT 1			
4	5	4	VISIT 1			
5	3	5	VISIT 1			
6	12		VISIT 1			
7	2		VISIT 1			
8	70		VISIT 1			
9	1.8		VISIT 1			
10		6	VISIT 2		NOT DONE	STUDY SITE FAILED TO ADMINISTER
11			VISIT 2	PHANTOM		
12			VISIT 2	PHANTOM		
13			VISIT 2	PHANTOM		
14			VISIT 2	PHANTOM		
15	2	7	VISIT 3			
16	1	8	VISIT 3			
17	1	9	VISIT 3			
18	16		VISIT 3			
19	2.5		VISIT 3			
20	75		VISIT 3			
21	3.2		VISIT 3			