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This Paper focuses on CDISC Questionnaires, Ratings and Scales (QRS) supplements and types of FDA Clinical Outcome Assessments

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ABSTRACT

CDISC develops SDTM (Study Data Tabulation Model) and ADaM (Analysis Data Model) QRS supplements that provide information on how to structure the data in a standard format for public domain and copyright-approved instruments. An instrument is a series of questions, tasks or assessments used in clinical research to provide a qualitative or quantitative assessment of a clinical concept or task-based observation. Controlled Terminology is also developed to be used with the supplements.

CDISC creates supplements for three types of instruments:

- Questionnaires
- Functional Tests
- Clinical Classifications

This Paper is an effort to

- Understand QRS supplements & how it is developed
- Understand how to model ratings and scales other than questionnaires,
- Understand ADaM Structure to be used for QRS supplements
- Understand different types of FDA Clinical Outcome Assessment (COA)'s
    - Clinician-reported outcome (ClinRO)
    - Observer-reported outcome (ObsRO)
    - Patient-reported outcome (PRO)
    - Performance outcome (PerfO)
- Understand how CDISC QRS Supplements assist in structuring COA data so that it is collected and reported in a standardized format.

INTRODUCTION

FDA considers the use of patient input an important part of medical product development that can foster innovation and the availability of safe and effective medical products. Patient input can be included in not only the selection of clinical outcomes but also to ensure the appropriateness of instruments used to collect trial data.

Patient experience data plays a critical part in medical product development by helping to ensure investigations of the effect of treatments assess outcomes that are meaningful to patients.

In instances where patient input cannot be obtained or reported reliably (e.g., young children, individuals with cognitive problems), other stakeholder input (e.g., a clinician or other trained health care professional and/or primary caregiver(s)) can provide important information regarding what is most valuable to assess in patients. As a result, information on clinical benefit or risk from the patients' perspective can be included in labeling or communicated in a way that is accurate and not misleading. Also, patient input can help inform benefit-risk assessment for regulatory decision making.

FDA discusses the need for outcome measures that are defined as part of the Drug Development Tools Qualification Program for COA instruments.

CDISC QRS Supplements assist in structuring COA data so that it is collected and reported in a standardized format.

FDA CLINICAL OUTCOME ASSESSMENT (COA)

A COA is any assessment that may be influenced by human choices, judgment, or motivation and may support either direct or indirect evidence of treatment benefit. COAs depend on the implementation, interpretation, and reporting from a patient, a clinician, or an observer.

Sponsors should determine early in medical product development whether they plan to use COAs in their clinical trials and plan for early interactions with regulatory bodies to obtain feedback about their COA measurement strategy from the relevant review division.

FDA uses COAs to determine whether a medical product has been shown to provide clinical benefit to patients. When clinical benefit is demonstrated, a description of that benefit can be provided in labeling or communication in terms of the concept or outcome measured (i.e., the aspect of an individual's clinical, biological, physical, functional state, or experience that the assessment is intended to capture).

There are different types of COAs.

- Clinician-reported outcome (ClinRO)
- Observer-reported outcome (ObsRO)
- Patient-reported outcome (PRO)
- Performance outcome (PerfO)

There are certain types of COAs derived from mobile health technologies (e.g., activity monitors, sleep monitors) that do not fall into one of the other types of COAs. Figure 1 describes different types of COAs.

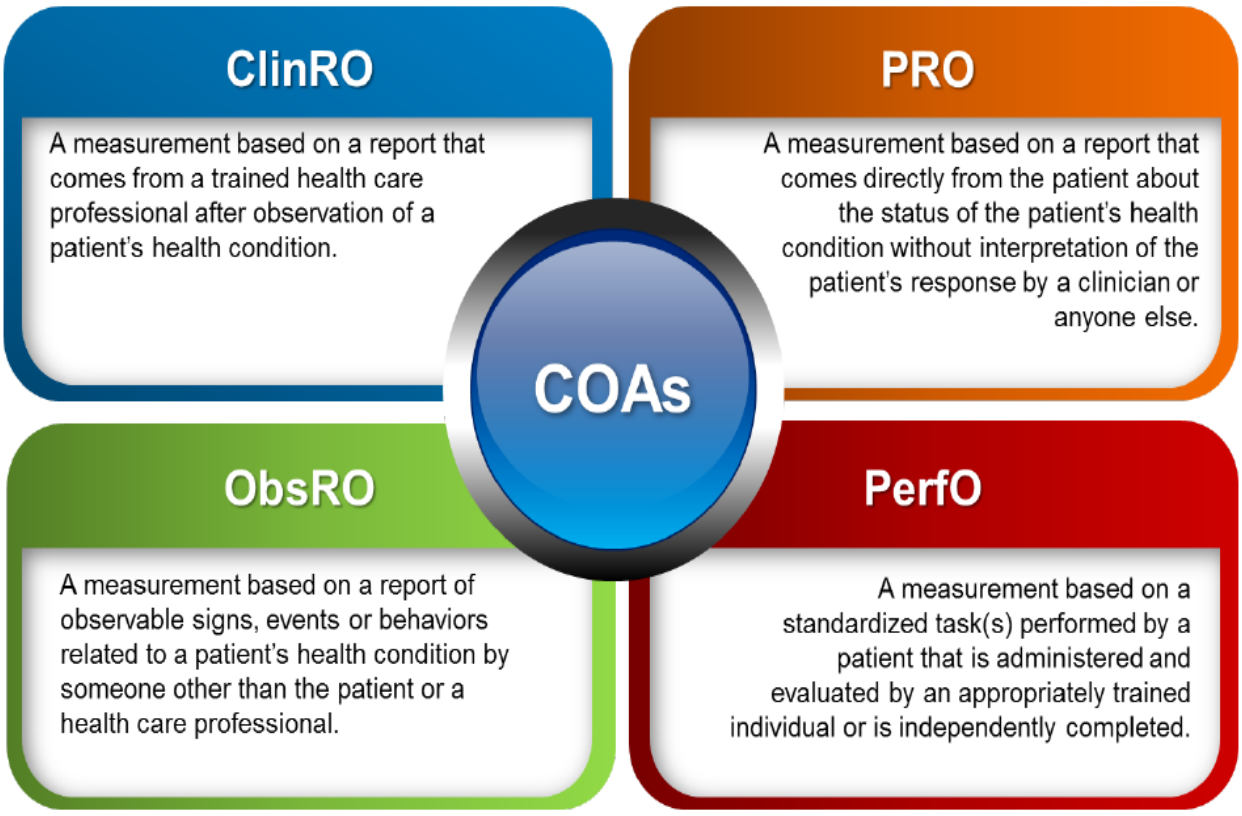


Figure 1. Overview of COA types

Clinician-reported outcome (ClinRO):

- Reflects evaluation of a patient's health condition by a healthcare professional.
- Involves clinical judgment or interpretation of the observable signs, behaviors, or other physical manifestations thought to be related to a disease or condition. Example: The Hamilton Depression Rating Scale 6 - Clinician Version.

Observer-reported outcome (ObsRO):

- An ObsRO is a measurement based on an observation by someone other than the patient or a health professional. This may be a parent, spouse, or other non-clinical caregiver who is in a position to regularly observe patient in daily life and report on a specific aspect of the patient's health. This does not include medical judgment or interpretation.
- For patients who cannot respond for themselves (e.g., infants or cognitively impaired), it is encouraged that observer reports only those events or behaviors that can be observed. As an example, observers cannot validly report an infant's pain intensity (a symptom) but can report infant behavior thought to be caused by pain (e.g., crying). Example: Disability Assessment for Dementia (DAD).

Patient-reported outcome (PRO):

- A PRO is a measurement based on a report that comes from the patient (i.e., study subject) about the status of a patient's health condition without amendment or interpretation of the patient's report by a clinician or anyone else.
- Symptoms or other unobservable concepts known only to the patient (e.g., pain severity or nausea) can only be measured by PRO measures. Example: Sheehan Disability Scale (SDS).

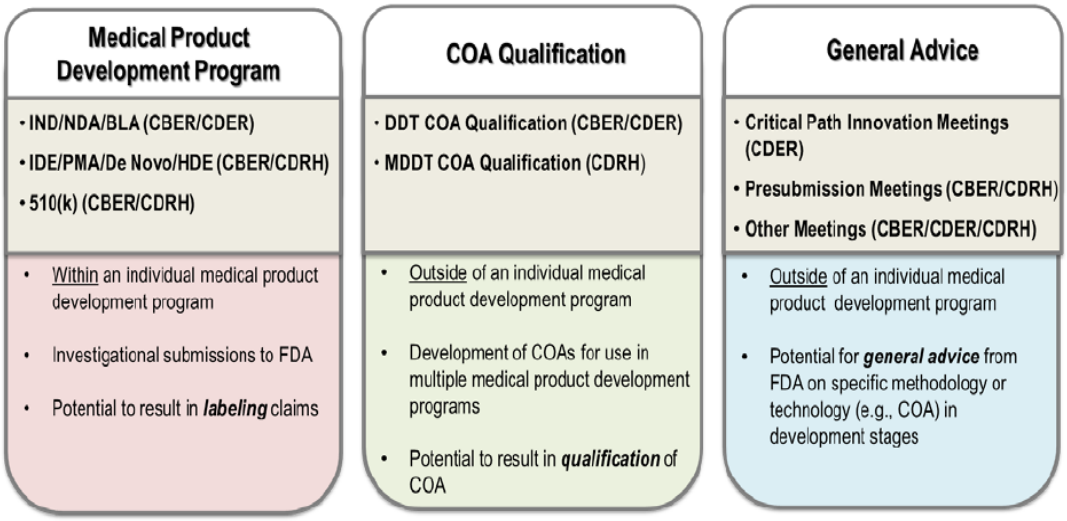
Performance outcome (PerfO):

- A PerfO is a measurement based on a task(s) performed by a patient according to instructions that is administered by a health care professional. Performance outcomes require patient cooperation and motivation. Example: 6 Minute Walk Test (SIX MINUTE WALK).

Center for Drug Evaluation and Research (CDER) COA Qualification Program:

- Manages the qualification process for COAs intended to address unmet public health needs.
- Works directly with requestors in guiding COA development for qualification.
- Encourages a collaborative, multidisciplinary setting where CDER can review COAs and provide advice on the development or modification of COAs outside the IND/NDA/BLA pathway.
- COA qualification is a regulatory conclusion that the COA is a well-defined and reliable assessment of a specified concept of interest for use in adequate and well-controlled (A&WC) studies in a specified context of use.
- COA qualification represents a conclusion that within the stated context of use, results of assessment can be relied upon to measure a specific concept and have a specific interpretation and application in drug development and regulatory decision-making.
- It is not mandatory to use ONLY qualified COAs for clinical trials. However, FDA believes that there are benefits to using a qualified COA. It encourages discussing with the appropriate FDA review division as early as possible on use of COAs in an individual drug development program.

- Figure 2 describes different pathways in which sponsors may obtain advice on COAs.



BLA = Biologics Licensing Application; **COA =** Clinical Outcome Assessment; **DDT =** Drug Development Tool; **HDE =** Humanitarian Device Exemptions; **IDE =** Investigational Device Exemption; **IND =** Investigational New Drug; **MDDT =** Medical Device Development Tool; **NDA =** New Drug Application; **PMA =** Pre-Market Approval

Figure 2. Different Pathways for Regulatory Advice on COAs

- In approaching selection or development of a COA, it is important to have an adequate understanding of the disease under investigation and conceptualization of clinical benefit from the targeted treatment effect.
- Figure 3 outlines the general approach to select and/or develop/modify COAs for clinical trials.

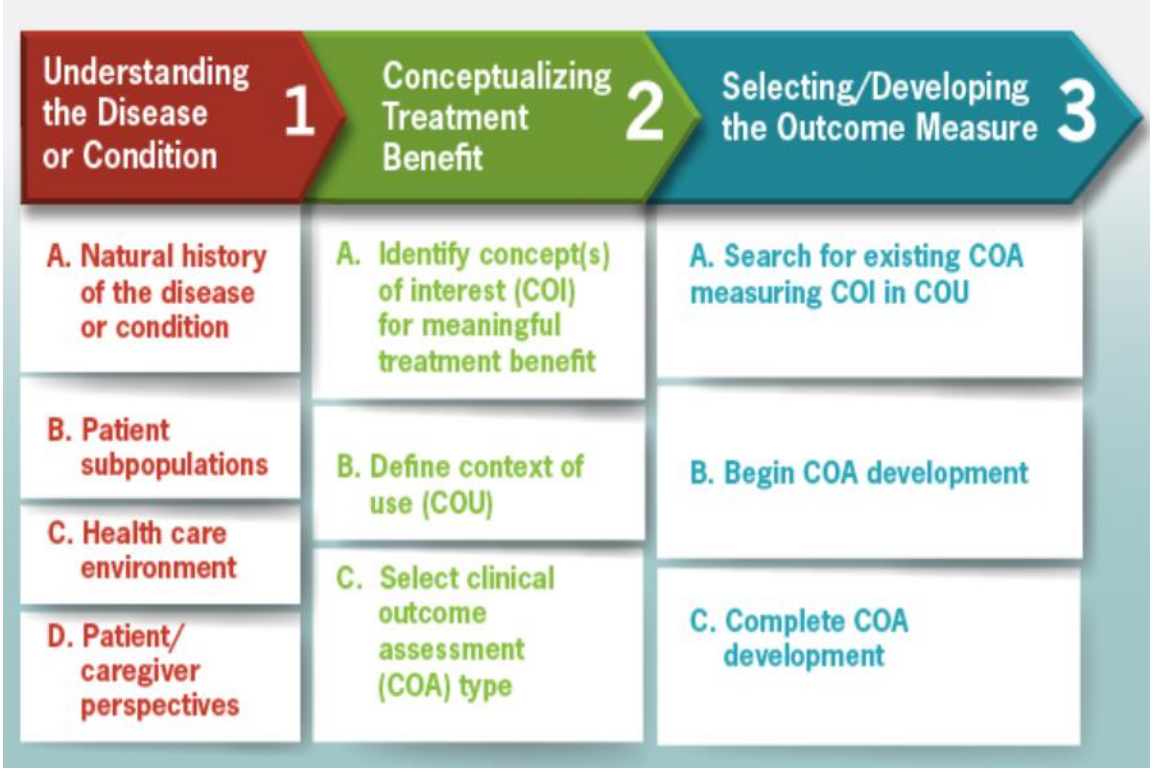


Figure 3. Roadmap to COA Selection/Development for Clinical Trials

Endpoint Positioning:

- The adequacy of a COA depends on its role and relationships with planned clinical trial endpoints. For example, regarding endpoint positioning, a high degree of certainty and validation is particularly important for a COA to be used in the context of a primary or co-primary endpoint.
- FDA recommends that sponsors carefully consider the order of COAs in the endpoint hierarchy. Sponsors should provide a proposed endpoint hierarchy for discussion with the FDA early in medical product development, with the understanding that it may evolve.
- In Figure 4, COAs are used as supportive endpoints with a physiologic measure as the primary endpoint intended to support an indication for treatment of a disease

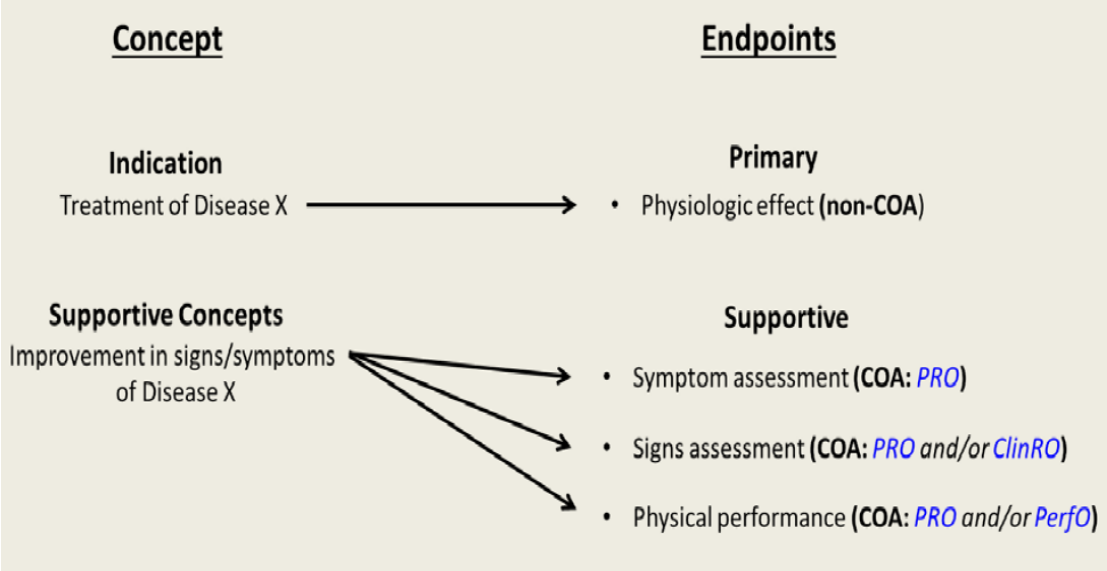


Figure 4. COAs used as supportive endpoints

- In Figure 5, COA is the primary clinical trial endpoint intended to support an indication for the treatment of symptoms associated with Disease Y

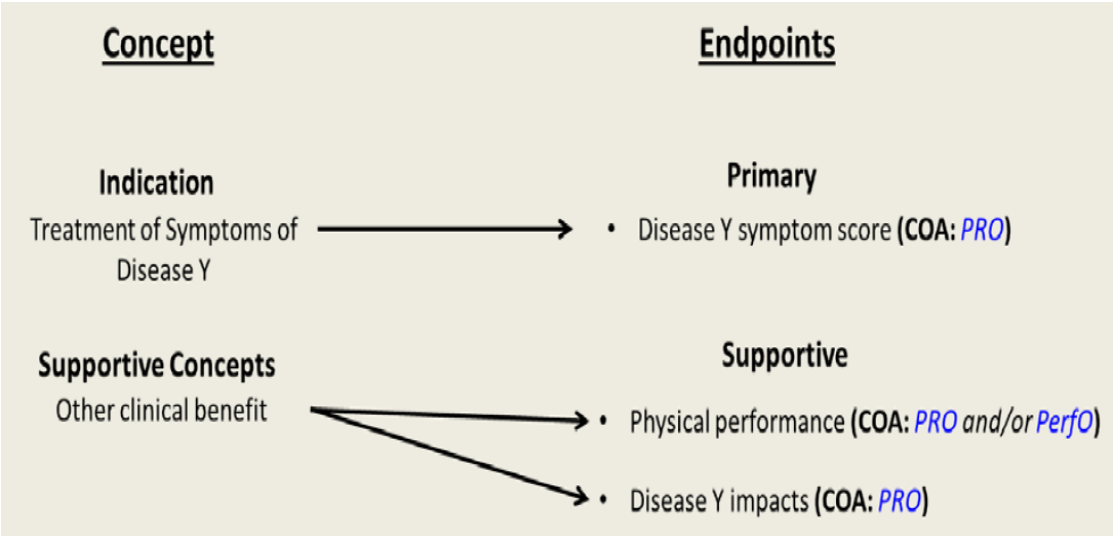


Figure 5. COA as primary clinical trial endpoint

Process to select, develop or modify a COA:

Figure 6 outlines the process of how to determine whether to use an existing instrument, modify an instrument, or develop a new instrument. This figure also summarizes the iterative process used in developing and/or modifying a COA for use in clinical trials for medical products.

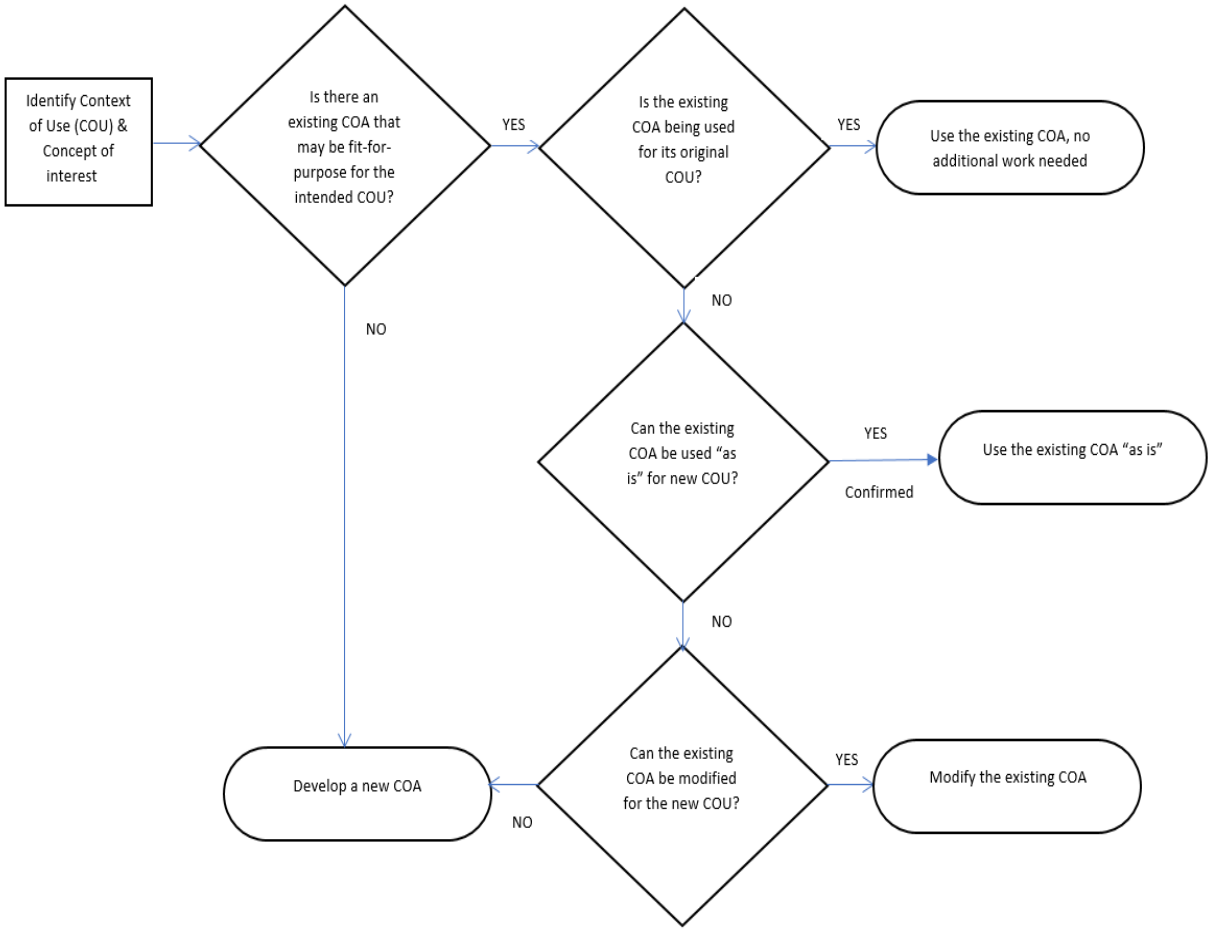


Figure 6. Process to select, develop or modify a COA

Meaningful Within-Patient Change vs. Between-Group Mean Differences:

- Individual within-patient change is different than between-group mean difference or treatment effect. From a regulatory standpoint, FDA is more interested in what constitutes a meaningful within-patient change in scores from the patient perspective (i.e., individual patient level).
- The between-group mean difference is the difference between the average score change between two study arms that is commonly used to evaluate treatment difference, but it does not address the individual within-patient change that is used to evaluate whether a meaningful score change is observed. A treatment effect is different than a meaningful within-patient change.

Blinding (Masking):

- The protocol should specify who will evaluate the COA endpoints, outcomes, or measurements in relation to the subjects (e.g., the investigator or an independent evaluator/rater) as well as who the intended reporter of patient information will be (e.g., clinicians, patients or caregivers) and to what extent blinding (masking) will be maintained among the investigators, evaluators/raters and reporters (e.g., clinicians, patients or caregivers).

- If masking is not possible (e.g., open-label study) and a COA is being proposed as a primary or key secondary endpoint in the endpoint hierarchy, the study design may limit interpretation of data from the COA. Patients' and/or clinicians' knowledge of treatment assignment may lead to systematic overestimation or underestimation of the treatment effect, the magnitude of which is unknown.

Patient-Level Missing COA Data:

- Even with the best planning, patient-level COA data may be missing at the end of the clinical trial.
- Sponsors should provide patients adequate education on the purpose of collecting the COA data to encourage patient compliance with completing COAs and help prevent and reduce the frequency of potential missing data in the first place.
- The protocol and the SAP should address plans for how the statistical analyses will handle missing COA data when evaluating clinical benefit and when considering patient success or patient response.

CDISC QRS SUPPLEMENTS

FDA Clinical Outcome Assessment (COA) program and QRS supplements:

- CDISC QRS Supplements assist in structuring COA data so that it is collected and reported in a standardized format.
- Below Table 1 illustrates how the **CDISC QRS supplements correlate with the FDA COA program**

	FDA COA			
CDISC SDTM QRS Supplements	**ClinRO**	**ObsRO**	**PRO**	**PerfO**
Questionnaires	X	X	X	
Functional tests				X
Clinical Classifications	X	X		

Table 1. This table illustrates how the CDISC QRS supplements correlate with the FDA COA program

QRS Supplement Contents:

- QRS supplements to the SDTMIG (Study Data Tabulation Model Implementation Guide) include instrument-specific Controlled Terminology and an SDTM example illustrating the use, applicable supplemental qualifiers and item-level mapping instructions for the results.
- The Functional Tests (FT) and the Disease Response and Clin Classification (RS) findings domains for ratings and scales were included from SDTMIG Version 3.3.
- QRS supplements to the ADaMIG (Analysis Data Model Implementation Guide) describe how to structure the questionnaire analysis data set. It includes sample analysis descriptions, scoring for the statistical analysis plan, data checks, and examples of analysis data set metadata, analysis variable metadata, and value-level metadata.
- A QRS supplement generally contains an annotated Case Report Form (aCRF) as well as guidance for mapping to the CDISC standards, whether those are CDASH (Clinical Data Acquisition Standards Harmonization), SDTM and/or ADaM.
- Each supplement may have more than one version and it is recommended that the latest version should always be selected where available.

CDISC creates QRS supplements for three types of instruments:

- ***Questionnaires:***
  - Questionnaire instruments are stored in the Questionnaires (QS) domain
  - Questionnaires often have a defined standard structure, format, and content.
  - Questionnaires consist of conceptually related items that are typically scored
  - Questionnaires consist of defined questions often with a defined set of potential answers.
  - Most often, the primary purpose of questionnaires is to generate quantitative statistic to assess a qualitative concept.
  - Table 2 represents the generic example of how the QS domain is to be populated for a fictional Fruit Preference questionnaire following the QRS Naming Rules. The questionnaire has responses from Strongly Disagree to Strongly Agree (0-4).

Row	STUDYID	DOMAIN	USUBJID	QSSEQ	QSTESTCD	QSTEST	QSCAT	QSORRES	QSSTRESC	QSSTRESN	QSLOBXFL	VISITNUM	QSDTC
1	STUDYX	QS	P0001	1	FPQ01001	FPQ01-I Like Apples	FRUIT PREFERENCE QUESTIONNAIRE	Strongly Agree	4	4	Y	1	2012-11-16
2	STUDYX	QS	P0001	2	FPQ01002	FPQ01-I Like Oranges	FRUIT PREFERENCE QUESTIONNAIRE	Disagree	1	1	Y	1	2012-11-16
3	STUDYX	QS	P0001	3	FPQ01003	FPQ01-I Like Bananas	FRUIT PREFERENCE QUESTIONNAIRE	Agree	3	3	Y	1	2012-11-16

Table 2. QS domain populated for a questionnaire

- ***Functional Tests:***
  - Functional Test instruments are stored in the Functional Tests (FT) domain and are named, standalone task-based evaluations, designed to provide an assessment of mobility, dexterity, and/or cognitive ability.
  - A Functional Test is not a subjective assessment of how the subject generally performs a task. Rather, it is an objective measurement of the performance of the task by the subject in a specific instance.
  - Functional Tests have documented methods for administration and analysis and require a subject to perform specific activities that are evaluated and recorded. Most often, Functional Tests are direct, quantitative measurements.
  - Table 3 represents the generic example of how the FT domain is to be populated for a fictional 40 Yard Dash functional test at 3 different visits following the QRS Naming Rules

Row	STUDYID	DOMAIN	USUBJID	FTSEQ	FTTESTCD	FTTEST	FTCAT	FTORRES	FTORRESU	FTSTRESC	FTSTRESN	FTSTRESU	FTLOBXFL	VISITNUM	FTDTC
1	STUDYX	FT	P0001	1	FYD01001	FYD01-Time	FORTY YARD DASH	5.2	sec	5.2	5.2	sec	Y	1	2012-11-16
2	STUDYX	FT	P0001	2	FYD01001	FYD01-Time	FORTY YARD DASH	5	sec	5	5	sec		2	2012-11-23
3	STUDYX	FT	P0001	3	FYD01001	FYD01-Time	FORTY YARD DASH	4.9	sec	4.9	4.9	sec		3	2012-11-30

Table 3. FT domain populated for a functional test

- ***Clinical Classifications:***
  - Clinical Classifications are based on a trained healthcare professional's observation of a subject's health condition or status with input from associated clinical records review.
  - Clinical Classifications may be based solely on objective data from clinical records, or they may involve a clinical judgment or interpretation of the directly observable signs, behaviors, or other physical manifestations (labs, vital signs, or clinical events) related to a condition or subject status.
  - If the instrument is a Rating or Grading Scale in which the intent of the instrument is to evaluate multiple body systems and all Composite Score type instruments, then they would be represented as a Clinical Classification in the RS domain.

- If the instrument is a Rating or Grading Scale in which the intent of the instrument is to evaluate a single body system, it would be stored in the morphology/physiology domain, which represents that body system.
- Table 4 represents the generic example of how the RS domain is to be populated for a fictional Smith Snoring Scale clinical classification at one visit.

Row	STUDYID	DOMAIN	USUBJID	RSSEQ	RSTESTCD	RSTEST	RSCAT	RSORRES	RSSTRESC	RSSTRESN	RSLOBXFL	RSEVAL	VISITNUM	RSDTC
1	STUDYX	RS	P0001	1	SSS01001	SSS01-Snoring Volume	SMITH SNORING SCALE	loud	3	3	Y	SPOUSE	1	2012-11-16
2	STUDYX	RS	P0001	2	SSS01002	SSS01-Snoring Extent	SMITH SNORING SCALE	25-50% of sleep time	2	2	Y	SPOUSE	1	2012-11-16
3	STUDYX	RS	P0001	3	SSS01003	SSS01-Snoring Pattern	SMITH SNORING SCALE	very regular	1	1	Y	SPOUSE	1	2012-11-16
4	STUDYX	RS	P0001	4	SSS01004	SSS01-Total Score	SMITH SNORING SCALE	6	6	6	Y	SPOUSE	1	2012-11-16

Table 4. RS domain populated for clinical classification

Process followed by CDISC to handle copyrighted instruments:

- CDISC must obtain permission to create a QRS supplement for copyrighted instruments. If this permission is not obtained, the supplement is not created.
- Granting CDISC the right to create supplements to represent an instrument in CDISC QRS domains is not a license for CDISC standards users to use the instrument without complying with the copyright holders licensing requirements.
- No part of a copyrighted instrument or accompanying guidelines may be reproduced, distributed, or transmitted in any form, or by any means, including photocopying, recording, or other electronic or mechanical methods without the permission of the copyright holder and payment of applicable fees.
- If a particular instrument is not having QRS supplement, one can request a QRS supplement be developed by completing the QRS Supplement Request Form in CDISC website

Different ADaM data structures that could be used for QRS supplements:

- ADaM Basic Data Structure (BDS): An analysis data set that contains one or more records per subject, per analysis parameter, per analysis time point. The parameters are mapped from --TEST and --TESTCD, and additional parameters are created as needed for derived scores.
- ADAM Other may also be used when the analysis has special needs that are not met by the BDS structure.

CONCLUSION

This Paper was an effort to understand types of FDA Clinical Outcome Assessment (COA)'s (Clinician-reported outcome (ClinRO), Observer-reported outcome (ObsRO), Patient-reported outcome (PRO) and Performance outcome (PerfO)), process of selection & development of COAs.

Clinical Outcome Assessment (COA)'s could be measured and analyzed in a stable and reliable ways, though there are still potential issues that need special attention. Reducing missing data during study conduct is more important and helpful to ensuring a reliable outcome.

CDER COA qualification represents a conclusion that within the stated context of use, results of an assessment can be relied upon to measure a specific concept and have a specific interpretation and application in drug development and regulatory decision-making.

This paper also explored on how CDISC QRS Supplements assist in structuring Clinical Outcome Assessment (COA) data so that it is collected and reported in a standardized format. In addition to the long-standing Questionnaires (QS) Domain, we have new domains identified by CDISC and incorporated into the SDTMIG. i.e., The Functional Tests (FT) and the Disease Response and Clin Classification (RS) findings domains for ratings and scales.

As a next step, we have a number of opportunities to advance the understanding and increase the use of COA's in the clinical setting, in multinational trials, and in regulatory review processes.

Patients are true experts in their disease and have insights that are impossible to determine without their direct input. It is clear one has to start with an understanding of the impact of the disease on the people who have it, and what they value most in terms of alleviation before you setup a measurement and go forward with truly patient-focused drug development.

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