CDISC 2023 European Interchange

a. Clinical trials in contemporary Africa and RWE/RWD
b. Associated Persons' Data and Domains
c. CDISC QRS Standards

Antonio Gabriele
Statistical SAS Programmer

OPIS
A Science Driven Biotech Focused CRO

a. Clinical trials in contemporary Africa and RWE/RWD

An interesting theme

- 50% of the global burden of disease, mostly due to infections, reside in sub-Saharan Africa
- Host to 17.5% of the global population, the African continent is dramatically underrepresented in clinical trials – only between 2.5–10% of clinical trials
- Majority of trials occur in South Africa or Egypt
- Focus on infectious diseases such as HIV and tuberculosis
- However public health focus expanding to noncommunicable diseases

OPIS
A Science Driven Biotech Focused CRO

Which solutions?

Digitalization

- **Employing** the **Use** of **Digital Health Technologies (DHTs)** for Effective and Efficient Recruitment of Patients
- Full **benefits** of digital technologies to **strengthen** the **health systems** are yet to be fully defined due to critical challenges in the sector
- **Challenges** include weak health systems governance, weak infrastructural investments, inadequate resources, weak human resource capacity, high cost of scaling-up and coordination issues, among others
- **Lack** of **systems thinking**, and design have significant impact on coordination of efforts resulting in fragmentation among various applications
- **Electronic medical record (EMR) data**, the use of **big data technologies**, the use of **automation** can be utilized to overcome the challenges of clinical trial recruitment.

Decentralization

- Decentralization in clinical research has partly been driven by the **need** to increase **diversity** and **inclusion** among trial **patients**
- Making easier to find **eligible** patients, and it **encourages** those **patients** to **participate** by reducing the amount of time they spend traveling
- Pointing out **local pharmacies**, **primary care providers** and **community health centers** as extensions of major research centers
- Widening **eligibility criteria**, tapping into **community-based medical centers**, and relying on patient sustain and "**promotion**"

Discourse

- Clinical Research should demonstrate both social and scientific value to **ensure** effective **stakeholder engagement**
- Trial sponsors must **ensure** that **pre-trial activities** must give room to accommodate a robust stakeholder engagement as key to project support

RWD and RWE: FDA definitions

Real World Data:

Real-World Data (RWD) are the data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.

Real World Evidence:

Real-world evidence is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD.

RCT studies:

- Protocol Design
- Homogeneous study population
- Limited to drug under evaluation
- Investigator driven
- Far from real life

RWD studies:

- Real World Setting
- Heterogeneous study population
- Various treatment option
- Healthcare Physician driven
- Close to real life

OPIS

n Biotech Focused CRO

RWE and RWD: different data sources

Data produced by physicians:

- Patient registries and cohorts
- Medication orders
- Medical reports

Data generated during routine patient care:

- Databases (medical, administrative, etc.)
- Electronic health records

Data produced by patients:

- Online studies with self-reported data from patients
- Internet of Things (connected object/ medical device/ wearable device)
- Social networks
- Mobile apps

OPIS

A Science Driven Biotech Focused CRO

Data Standardization of DHTs

- **DHTs** are defined as an electronic method, system, product, or process that generates, stores, displays, processes and/or uses data within a healthcare setting [EFPIA].

Challenges

- DHTs produce a wealth of data, but there is ambiguity in where and how the data will be accessed, transformed and collected in clinical trial.
- Previously, data was manually collected per study and not standardized across trials.

Opportunities

- Data standardization enables to efficiently scaling up the integration and analysis of data:
  - compliant with health authorities requirements.
  - in conjunction with other clinical data and ready for secondary usage.

OPIS

A Science Driven Biotech Focused CRO

b. Associated Persons' Data and Domains

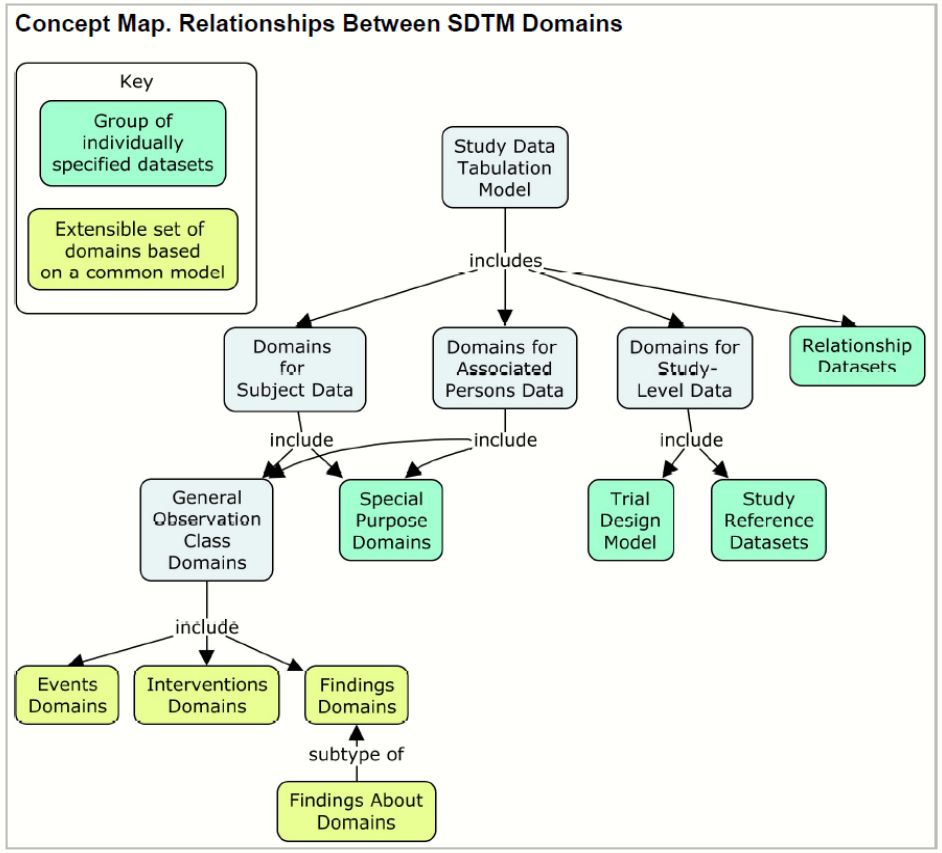
- Data may be collected about persons other than the subject under study
  - Associated persons are not themselves subjects in the trial, but data is collected about them
  - The data are about the **Associated Person**, not the subject (or device)
  - The associated person does not have a subject identifier (SUBJID)

- It is necessary to distinguish associated person's data and keep AP data separate from subject data in submission
  - Associated Persons datasets are given a prefix of **AP–**
  - Associated Persons records require the population of the **APID** (Associated Persons Identifier) variable
  - **APDM** is not a required domain for associated person.

Subject Data vs Associated Persons' Data (1)

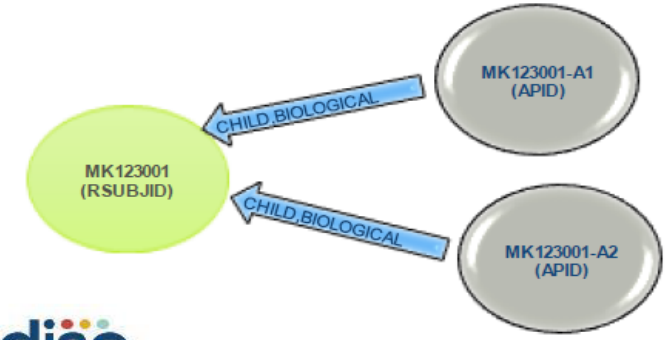
- Domains which describe the progress of a subject through a study(SE, SV, DS etc.) are not relevant for associated persons because such persons are not in the study.
- The following variables would not generally be used in AP domains because they are usually only applicable to subjects in the study:

  - RFSTDTC
  - RFXSTDTC
  - RFICDTC
  - ARMCD
  - ACTARMCD
  - RFENDTC
  - RFXENDTC
  - RFPENDTC
  - ARM
  - ACTARM



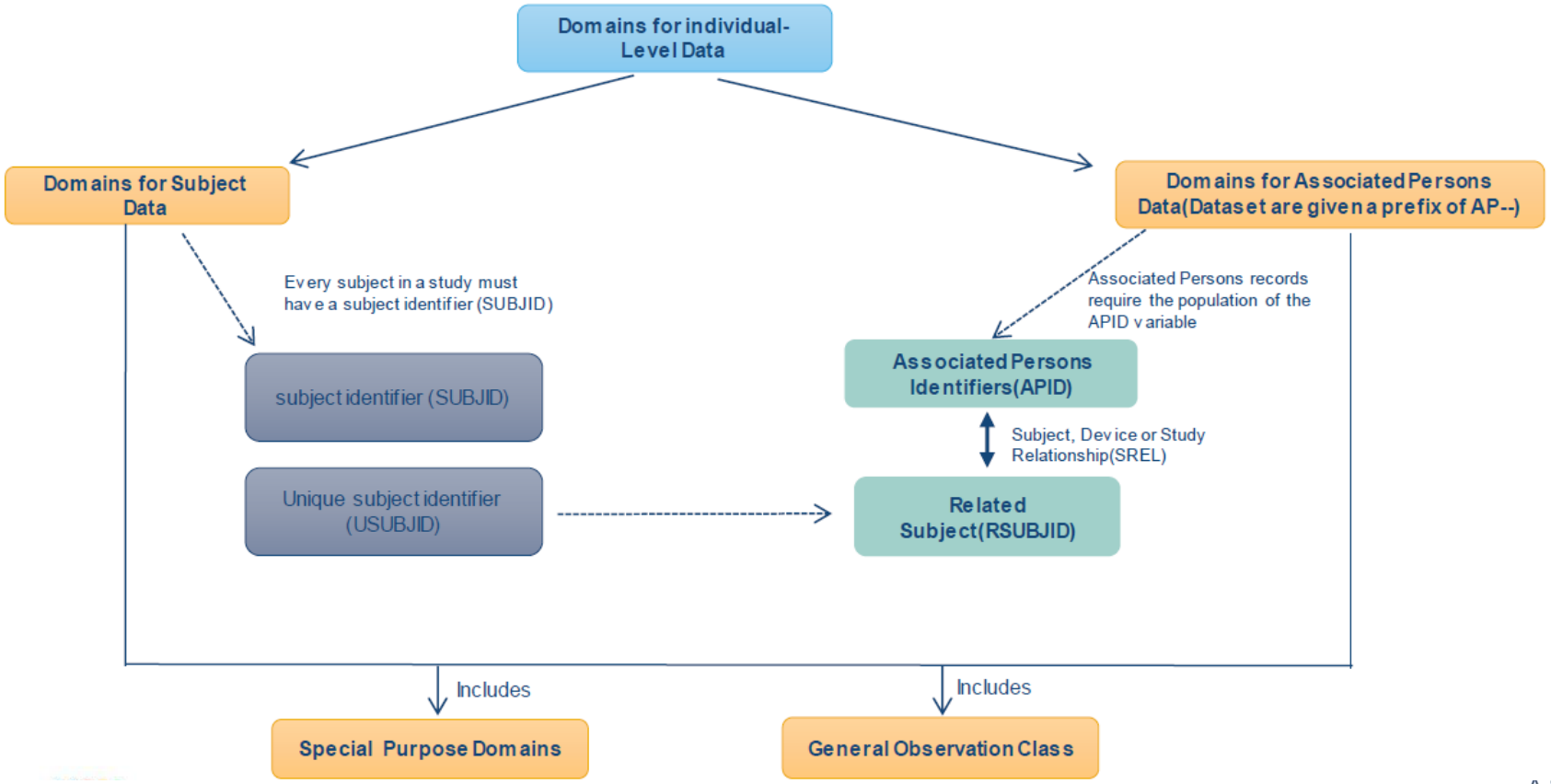
OPIS
A Science Driven Biotech Focused CRO

Subject Data vs Associated Persons' Data (2)



A mother gave birth to twins and the assigned associated person identifiers (APIDs) to infants by following a dash plus a letter and a number ("--A1" and "-A2") to the mother's USUBJID.

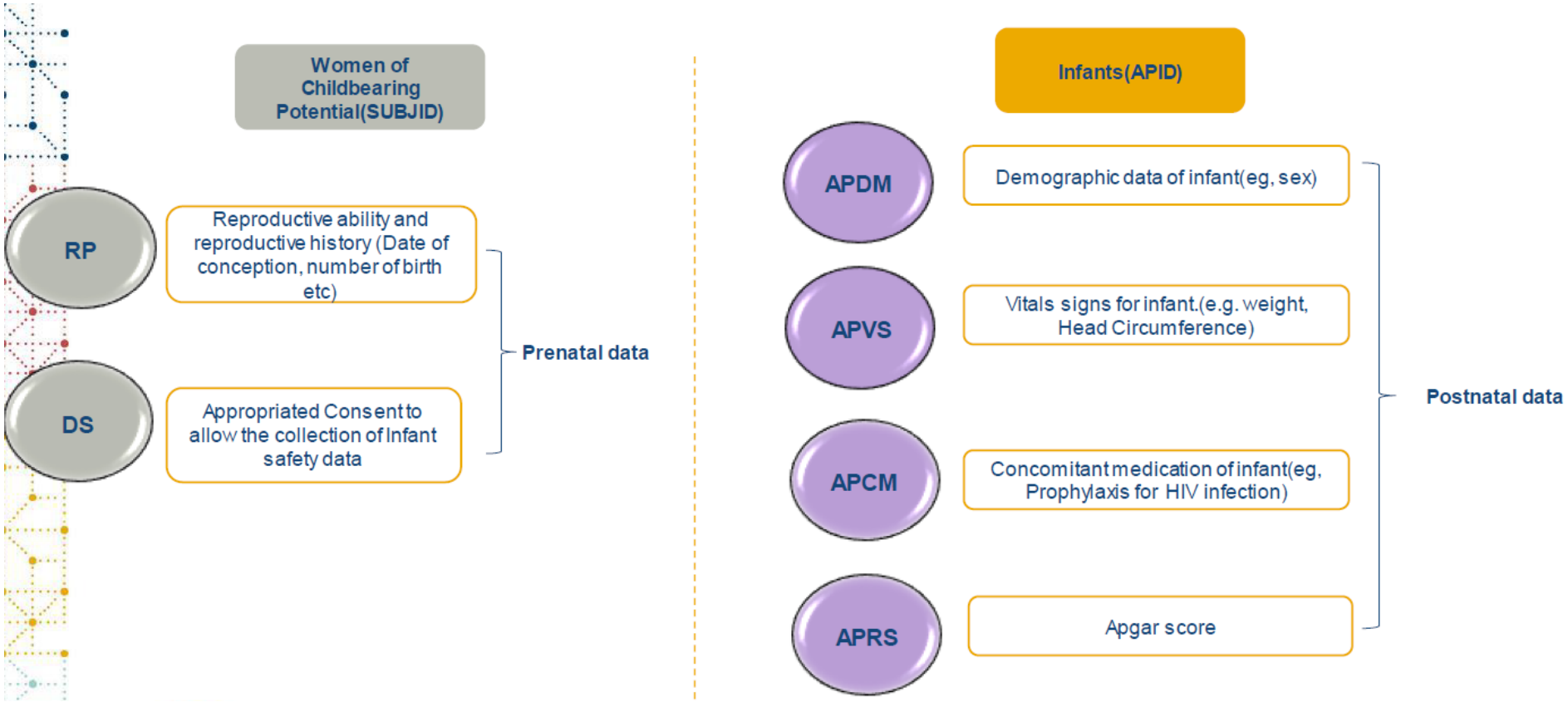
STUDYID	DOMAIN	APID	RSUBJID	SREL	SEX
MK123	APDM	MK123001-A1	MK123001	CHILD, BIOLOGICAL	M
MK123	APDM	MK123001-A2	MK123001	CHILD, BIOLOGICAL	F



A Science Driven Biotech Focused CRO

Infant Safety Data Collection in HIV Study

- HIV Studies will enroll women of Childbearing Potential as the subject.
- When a subject is pregnant or becomes pregnant, it is important and may be necessary to collect both prenatal and postnatal data on the infant pertaining to overall health and HIV status.
- Infant safety data collection provides the ability to monitor growth and development of the infant as well as potential adverse effects that may be associated with prenatal drug exposure.



OPIS
A Science Driven Biotech Focused CRO

c. CDISC Standards for QRS

Questionnaires, Ratings and Scales (QRS) - Each QRS 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

The QRS team develops Controlled Terminology and SDTM (tabulation) supplements; the ADQRS Team develops ADaM (analysis) supplements

CDISC creates supplements for four types of instruments:

- **Questionnaires**: Questionnaire instruments are stored in the Questionnaires (QS) domain
- **Functional Tests**: Functional Test instruments are stored in the Functional Tests (FT) domain
- **Clinical Classifications and Disease Response**: Clinical Classifications and Disease Response instruments or criteria are represented in the Disease Response and Clin Classification (RS) domain.

QRS | CDISC

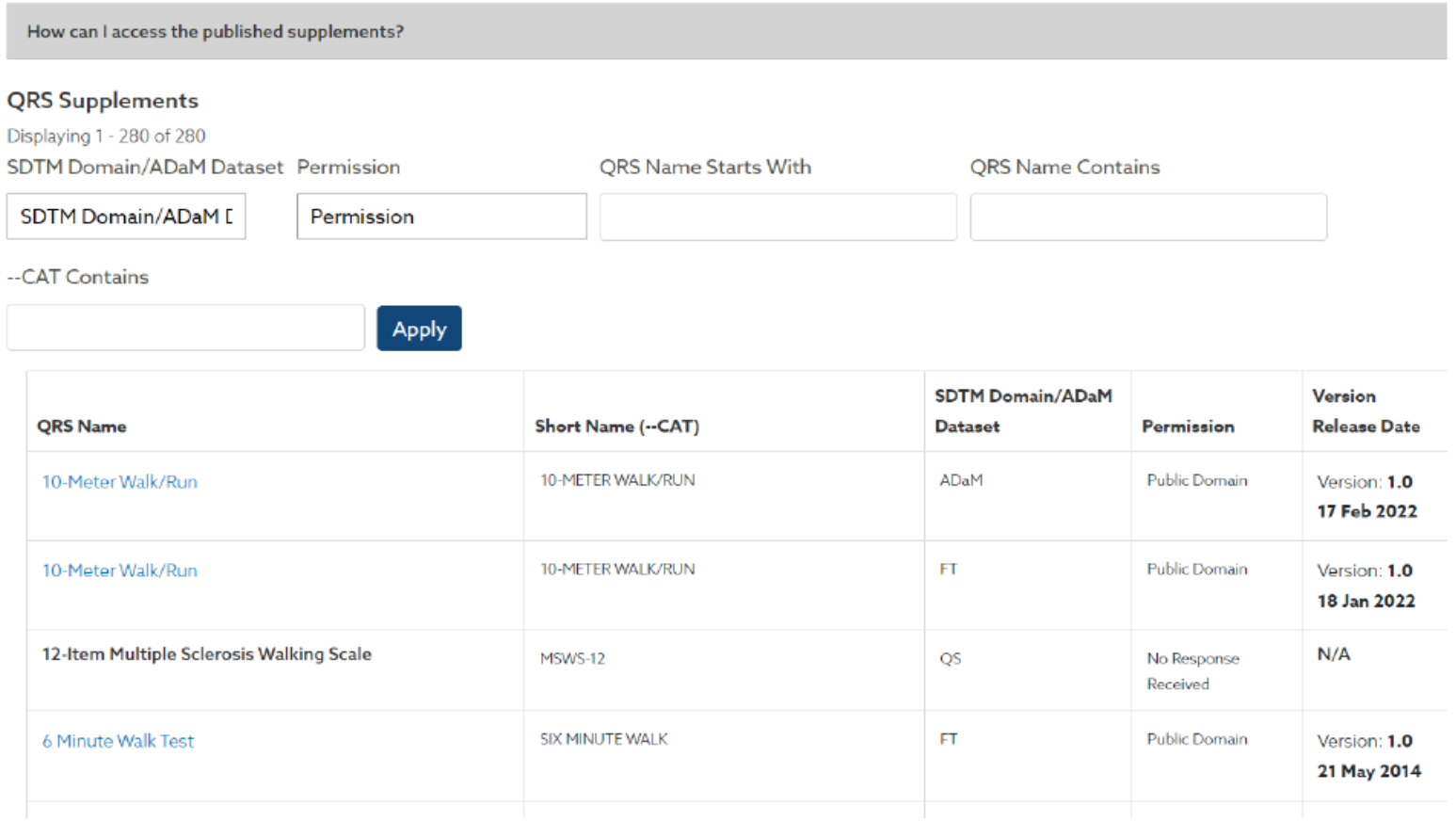
QRS Standards –QRS Supplements

QRS Types:

- >10 Functional Tests,
- About 50 Clinical Classifications
- >100 Questionnaires

Disease areas most frequently covered:

- Mental health
- Neurology
- Endocrine



QRS Name	Short Name (--CAT)	SDTM Domain/ADaM Dataset	Permission	Version Release Date
10-Meter Walk/Run	10-METER WALK/RUN	ADaM	Public Domain	Version: **1.0** **17 Feb 2022**
10-Meter Walk/Run	10-METER WALK/RUN	FT	Public Domain	Version: **1.0** **18 Jan 2022**
12-Item Multiple Sclerosis Walking Scale	MSWS-12	QS	No Response Received	**N/A**
6 Minute Walk Test	SIX MINUTE WALK	FT	Public Domain	Version: **1.0** **21 May 2014**

QRS | CDISC

OPIS

A Science Driven Biotech Focused CRO

QRS Handling practices (1)

Missing QRS Data

• When any individual QRS instrument item is not done, record for the item shall be populated in SDTM dataset with --STAT=”NOT DONE”

• When the whole QRS instrument assessment is not done, “QSALL”, “FTALL”, and “RSALL” shall **NOT** be used as the Test Code. Authorities recommended to address the missing QRS data ALWAYS at the individual item level

• –REASND shall be populated if the reason for NOT DONE is available, otherwise –REASND shall be set as null

Conditional Branching Concept

CDISC QRS team discussed with FDA and will be reviewed again 2Q23: if the item is not done due to conditional branching, SUPP datasets prepared to show Conditional Branching Item Indicator as “Y”

QRS Handling practices (2)

ORRESU/--STRESU Handling

- Units are pre-defined in the questions, --ORRESU/--STRESU values are populated
- Units are included in the predefined responses, --ORRESU/--STRESU are null

Total Score and Sub-total Score

• Subtotal and total scores are represented in--ORRES, --STRESC, and –STRESN
• If scores are received or derived by the sponsor, it is recommended that they are submitted to SDTM and verified in ADaM whenever feasible
• Details could be documented in SDRG and ADRG

About –DRVFL

Scenario	--DRVFL (derived flag)
Derived by the sponsor in EDC	Y (ORESS could be null)
Investigator calculate the score and written on a CRF	<null>
Received from external data supplier	<null>

Upcoming changes:
The SDS team is considering to deprecate the --DRVFL variable in SDTMIG V4.0.
CDISC QRS has stopped using it, all derived data are considered as captured data moving forward.

QRS Handling practices (3)

When --ORRES >200 characters

If Pre-defined response > 200 characters

Answer for Actual Attempts Only

Actual Lethality/Medical Damage:

0. No physical damage or very minor physical damage (e.g., surface
1. Minor physical damage (e.g., lethargic speech; first-degree burns
2. Moderate physical damage; medical attention needed (e.g., consc
   burns; bleeding of major vessel).
3. Moderately severe physical damage; *medical* hospitalization and
   intact; third-degree burns less than 20% of body; extensive blo
4. Severe physical damage; *medical* hospitalization with intensive c
   burns over 20% of body; extensive blood loss with unstable vi
5. Death

Selected on the instrument (>200 character)	QSORRES in mapping (shortened <=200 character)	QSSTRESC /QSSTRESN
Moderately severe physical damage; medical hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures)	Moderately severe physical damage; medical hospitalization and likely intensive care required	3
Severe physical damage; medical hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area)	Severe physical damage; medical hospitalization with intensive care required	4

Length of the text is shortened

If Free-text response >200 characters for field with –TESTCD assigned

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Prior to Study Entry: Time He/She Felt Most Suicidal	Since Study Start:
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐

Inappropriate to use the "shorten" approach. Additional text could be stored in SUPP.

OPIS
A Science Driven Biotech Focused CRO