Clinical Classifications: Getting to know ‘the new kid on the QRS block’!
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ABSTRACT

Questionnaires, Ratings, and Scales (QRS) encompass 3 main concepts: Questionnaires (QS), Functional Tests (FT), and Clinical Classifications (RS) - the new kid on the QRS block. As with all things new, there may be some confusion in mapping Clinical Classifications, versus the other members of the QRS family. To add to this confusion, Clinical Classifications have recently been moved from QS to RS - a domain that was originally developed just for Oncology (Disease Response). Knowing the distinction between a Questionnaire and Functional Test, as well as what distinguishes them from a Clinical Classification is critical here. This presentation begins by introducing the members of the QRS family, and provides differences among them, by using a few published instruments for illustration. The Six Minute Walk and AUDIT-SR show how FT differs from QS. Then we introduce AIMS as a rather straightforward clinical classification, (one that was recently moved from QS to RS), and ATLAS is discussed to illustrate how clinical classifications utilize data from multiple domains. Finally, we present a sponsor-created VAS as another example of an instrument that, despite appearances, does not conform to QRS standards and is not mapped to QS. The general guidance for mapping, a decision tree map, and references that allow a more detailed understanding of clinical classifications sum up this paper on the QRS family.

INTRODUCTION

‘Questionnaires, Ratings, and Scales’ (QRS) 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. QRS instruments have a defined standard structure, format, and content, and consist of conceptually related items that are typically scored. They also have documented methods for administration and analysis. Most often, the primary purpose of a questionnaire is the generation of a quantitative statistic to assess a qualitative concept. Since the release of SDTM IG v3.3 QRS are now split into three domains - FT, QS, and RS - to distinguish the different types of instruments/assessments. There are supplements and controlled terminology (CT) developed by CDISC for individual questionnaires, ratings, and scales when the instrument is in the public domain or permission is granted by the copyright holder. Since it was first released, QRS guidance has evolved into a full suite of resources including Description, Supplements, FAQs, etc. that are available on the CDISC Website and Wiki. Over the last few years QRS guidance has become more streamlined, and things are more comprehensive now (i.e. the organization of QRS instruments, mappings, controlled terminology, etc.). Here’s a link to the standards: [https://www.cdisc.org/standards/foundational/qrs](https://www.cdisc.org/standards/foundational/qrs)

DIFFERENCES BETWEEN QS, FT, AND RS:

**QS:** A findings domain that contains data for named, stand-alone instruments designed to provide an assessment of a concept. Questionnaires consist of defined questions with a defined set of potential answers. They are conceptually related items that have a defined structure, format, and content, and are typically scored. The short name of the instrument is stored in QSCAT. Each question is stored in QSTEST, which provides a longer more informative label; while QSTESTCD houses the CDISC CT naming conventions for the code that identifies the instrument, version, and item number. The original result in QSORRES corresponds to the responses printed on the instrument or CRF. The numeric values of these responses are the standard numeric QSSTRESN and character QSSTRESC. The QRS supplements that describe this information can be found on the QRS page: [https://www.cdisc.org/standards/foundational/qrs](https://www.cdisc.org/standards/foundational/qrs) by filtering the “SDTM Domain/ADaM Dataset” box by “QS”.

**FT:** A findings domain that contains data for named, standalone task-based evaluations, designed to provide an assessment of mobility, dexterity, and/or cognitive ability. It differs from questionnaires in that tasks performed by the subject are objectively assessed by trained observers. The QRS CT naming rules mentioned above for QS, also apply to FT. FT examples can be found on the QRS page: [https://www.cdisc.org/standards/foundational/qrs](https://www.cdisc.org/standards/foundational/qrs) by filtering “SDTM Domain/ADaM Dataset” by “FT”.


RS: A findings domain that contains data for the assessment of disease response to therapy, or clinical classification based on published criteria. Clinical Classifications are named measures whose output is an ordinal or categorical score that serves as a surrogate for, or ranking of, disease status, symptoms, or other physiological or biological status. 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 related to a condition or subject status. RS supplement examples can be found on the QRS page: https://www.cdisc.org/standards/foundational/qrs by filtering "SDTM Domain/ADaM Dataset" by “RS”.

Clinical classifications, the new kid on the QRS block, differs from Questionnaires and Functional Tests in several ways. Clinical classifications:

1. Provide a surrogate for or ranking of disease status, or physiological or biological processes.
2. Can consist of composite ratings, laboratory results, vital signs measurements or any other aspect of disease / physiological / biological status, or any other predictive data source - as with the AIMS.
3. May appear less intuitive than questionnaires since the relation among predictors may be less obvious. The QRS instrument definition and usage determine whether any instrument is really a Clinical Classification; that would help you decide which CDISC domain it should map to. If a QRS instrument is used to provide status for a disease, disease severity or clinical endpoint, then it could be wholly or a part of a Clinical Classification. This may make Clinical Classifications more challenging to identify by appearance than the other two.

MAPPING CLINICAL CLASSIFICATIONS:

If you were using one of the previous versions of the SDTM IG - v3.2 or earlier, Clinical Classifications would have been mapped to the QS domain. The Abnormal Involuntary Movement Scale – Anchored (AIMS) provides a good example of such a clinical classification. However, that has changed with SDTM IG v3.3 wherein Clinical Classifications now map to the RS domain, which is now called ‘Disease Response and Clin Classifications’.

The AIMS is a 12-item instrument originally developed in the 1970s to measure Tardive Dyskinesia (TD), a disorder that develops as a side effect of long-term use with neuroleptic medications in treating some psychiatric conditions. It can easily be integrated into a routine clinical evaluation, with a score of 2 or more classifying the patient as having TD.
• AIMS as it was mapped to QS prior to SDTM IG v3.3:

<table>
<thead>
<tr>
<th>STUDYID</th>
<th>DOMAIN</th>
<th>USEBID</th>
<th>RSSEQ</th>
<th>RSTSTCD</th>
<th>RSTEST</th>
<th>RSSTCAT</th>
<th>RSSTCAT</th>
<th>RSORRES</th>
<th>RSSTRSC1</th>
<th>RSSTRSC2</th>
<th>RSSTREN1</th>
<th>RSSTREN2</th>
<th>RSSTREN3</th>
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<tr>
<td>STUDYX</td>
<td>QS</td>
<td>P0001</td>
<td>1</td>
<td>AIMS0101</td>
<td>AIMS01-Muscles of Facial Expression</td>
<td>AIMS</td>
<td>FACIAL AND ORAL MOVEMENTS</td>
<td>Minimal, may be extreme normal</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>STUDYX</td>
<td>QS</td>
<td>P0001</td>
<td>2</td>
<td>AIMS0102</td>
<td>AIMS01-Lips and Personal Area</td>
<td>AIMS</td>
<td>FACIAL AND ORAL MOVEMENTS</td>
<td>None</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>STUDYX</td>
<td>QS</td>
<td>P0001</td>
<td>3</td>
<td>AIMS0103</td>
<td>AIMS01-Jaw</td>
<td>AIMS</td>
<td>FACIAL AND ORAL MOVEMENTS</td>
<td>Mild</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>STUDYX</td>
<td>QS</td>
<td>P0001</td>
<td>4</td>
<td>AIMS0104</td>
<td>AIMS01-Tongue</td>
<td>AIMS</td>
<td>EXTREMITY MOVEMENTS</td>
<td>Moderate</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td></td>
<td></td>
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<td>P0001</td>
<td>5</td>
<td>AIMS0105</td>
<td>AIMS01-Upper Extremities</td>
<td>AIMS</td>
<td>EXTREMITY MOVEMENTS</td>
<td>Severe</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>STUDYX</td>
<td>QS</td>
<td>P0001</td>
<td>6</td>
<td>AIMS0106</td>
<td>AIMS01-Lower Extremities</td>
<td>AIMS</td>
<td>EXTREMITY MOVEMENTS</td>
<td>Mild</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
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<td>STUDYX</td>
<td>QS</td>
<td>P0001</td>
<td>7</td>
<td>AIMS0107</td>
<td>AIMS01-Neck, Shoulders, Hips</td>
<td>AIMS</td>
<td>TRUNK MOVEMENTS</td>
<td>Severe</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>STUDYX</td>
<td>QS</td>
<td>P0001</td>
<td>8</td>
<td>AIMS0108</td>
<td>AIMS01-Severity of Abnormal Movements</td>
<td>AIMS</td>
<td>GLOBAL JUDGMENTS</td>
<td>Minimal</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>STUDYX</td>
<td>QS</td>
<td>P0001</td>
<td>9</td>
<td>AIMS0109</td>
<td>AIMS01-Incapacitation due Abn Movements</td>
<td>AIMS</td>
<td>GLOBAL JUDGMENTS</td>
<td>None, normal</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

After the release of SDTM IG v3.3, this is what it looks like mapped to RS:

rs.xpt

CLINICAL CLASSIFICATIONS BASED ON MULTIPLE DATA SOURCES:

The Age Treatment with Systemic Antibiotics, Leukocyte Count, Serum Albumin, and Serum Creatinine as a Measure of Renal Function (ATLAS) is a clinical classification using data from Multiple Domains:

Age, treatment with systemic antibiotics, leukocyte count, serum albumin, and serum creatinine.
GUIDELINES FOR MAPPING CLINICAL CLASSIFICATIONS TO RS:

When using the RS domain to represent Clinical Classification measures that incorporate data from other domains (as in ATLAS):

- All source data must be represented in the topic-based domain(s) to which they pertain. For example, if a lab test is collected on the CRF and scored for a Clinical Classification, the lab test result must be recorded in LB and follow LB compliance rules.
- If the source value is directly collected on the Clinical Classification instrument, then the values from the source record may be transcribed to the corresponding RS record.
- If a Clinical Classification uses a source value by comparing it to a range (e.g., "2-5" or ">3"), then the source value will exist only in the source domain; the range is represented in the corresponding RS record in RSORRES.
- RSEVALID can be used in conjunction with RSEVAL for Clinical Classifications to provide additional detail of who is providing the assessment. When used with Clinical Classification data, RSEVALID may represent free text values. However, note that RSEVAL is not to be used in Disease Response criteria of RS.
- Totals and sub-totals in Clinical Classifications are considered collected data if recorded by an assessor.

WHEN TO MAP TO RS VERSUS FA OR A BODY SYSTEM DOMAIN:

Deciding where to map data could present a dilemma. Again, usage defines a Clinical Classification and should be the guide to mapping data. When the data collected on a CRF pertains to morphological measurements or physical assessments then the appropriate Body system domain should be mapped. However, when the assessment is about whether or how a subject performs a specific set of activities that help the investigator
determine the rank of, classify disease status, symptoms, or another physiological or biological status, then it should get mapped to RS as a Clinical Classification.

The Duchenne Muscular Dystrophy Therapeutic Area User Guide (TAUG) has 3 Clinical Classifications that provide a ranking or status of disease status:

- North Star Ambulatory Assessment (NSAA),
- Brooke Upper Extremity Rating Scale (BUERS)
- Vignos Lower Extremity Rating Scale (VLERS)

This TAUG also provides other measures that could be confused with a Clinical Classification:

- Bone Mineral Density Z-Score → MK (Musculoskeletal System Findings)
- Body Fat Percentage → MK (Musculoskeletal System Findings)
- Lean Body Mass → MK (Musculoskeletal System Findings)
- Raw maximal inspiratory pressure → RE (Respiratory System Findings)
- Percent predicted maximal inspiratory pressure → RE (Respiratory System Findings)

However, none of these provide a proxy for the status or ranking of a disease or physiological biological process. They provide a measure of a biological process and can be used by a Clinical Classification, but by themselves are not Clinical Classifications. These results are instead mapped to the appropriate body system domain rather than RS.

Prior to the release of SDTM IG 3.3, if a procedure was done and there was a disease status or a finding from the procedure, then this result - being inappropriate for PR domain, would map to FA. Another situation would be, if a sponsor developed a Visual Analog Scale (VAS - that are like QRS but would not be mapped to or not defined as a QRS domain) to provide a ranking of a disease then it would map to FA. For example, in the Psoriasis TAUG: Pgs. 20 & 21 show how a VAS instrument is mapped to FA - instead of RS.

With the advent of RS falling within QRS, any direct results / measurement pertaining to a certain body system would map to the respective findings domain and the classification would map to RS; for example: In a spirometry, the procedure, date and details about the procedure would map to PR, but the results from the procedure would map to a body system domain, and the objective measure or classification would map to RS. Depending on what kind of results are collected it could map to RE or MK or OE, depending on the information that’s being collected. An objective measure (based on observation) or classification of the disease state or condition or risk that is measured and scored, should be mapped to RS. If the procedure (Echocardiogram or Spirometry or Lung function test, etc.) hasn’t enough information to create PR, then it may map to the --METHOD variable within the body system domain. Alzheimer’s TAUG: Occurrences of PET or PET/CT procedures are recorded in the PR domain.

Rows 1-2: Show PET/CT head scans for two subjects using the same PET/CT scanner, as defined in SPDEVID. Row 3: Shows a PET scan of the head for a third subject.
EXAMPLES OF CLINICAL CLASSIFICATIONS (RS) THAT SPAN MULTIPLE BODY SYSTEMS:

(You would need to log in or create an account on the CDISC website to access these links)


- ASSIGN is another Clinical Classification that spans multiple body systems, however the difference here is that only composite score is captured in RS, whereas the data that is used for input to the scores remain in their original domain. The relationship between RS and the parent domain should be defined using RELREC: https://www.cdisc.org/standards/foundational/qrs/assign-risk-score

EXAMPLES OF FA AND OTHER BODY SYSTEM DOMAINS:

Another example of FA versus RS is, if you have a rash over the last 3 days and you want to measure the intensity of pain at its peak, or if there is an AE of interest then it would still reside in FA. On the other hand, if this were a clinical classification based on objective criteria from a published instrument, then the data would reside in RS.
TAUGs for Asthma and others show examples of data mapped to different body system domains like RE, MK, etc. See below an example from the Asthma TAUG for RE domain: This example shows results from several spirometry tests using either a spirometer or a peak flow meter where only the best result is available:

<table>
<thead>
<tr>
<th>Row</th>
<th>STUDYID</th>
<th>DOOMAIN</th>
<th>USUBJID</th>
<th>SEQ</th>
<th>ASEQ</th>
<th>AESEQ</th>
<th>AEPSID</th>
<th>AETERM</th>
<th>AEARM</th>
<th>AELOC</th>
<th>AEAT</th>
<th>AESEV</th>
<th>AESEER</th>
<th>AEACN</th>
<th>AESTOTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>XYZ</td>
<td>AE</td>
<td>XYZ-789</td>
<td>41969</td>
<td>5</td>
<td>Injection</td>
<td>site rash</td>
<td>General disorders and administration site conditions</td>
<td>ARM</td>
<td>LEFT</td>
<td>MILD</td>
<td>N</td>
<td>NOT APPLICABLE</td>
<td>2007-05-10</td>
<td></td>
</tr>
</tbody>
</table>

If the above results were used to provide a disease status for Asthma or physiological status for lung capacity, this could be mapped as a Clinical Classification.

THE QRS DECISION TREE MAP:

CONCLUSION:

This should now give you a good idea of how to distinguish Clinical Classifications from a Questionnaire or Functional Test. You should also be able to map the information to the appropriate domain(s) in SDTM.

Remember, that the usage of data collected and the version of the SDTM IG determines whether an instrument or series of questions is a Clinical Classification. Now that you’ve met ‘the new kid’ on the QRS block, you’ll hopefully be more comfortable working with this type of data.
ADDITIONAL INFORMATION, LINKS, AND RESOURCES:

- CDISC Controlled Terminology: Package 46 update: Use of QSMETHOD – for example, VAS (Visual Analog Scale) is a method added to the QRSMETHOD codelist. The QRSMETHOD codelist will support the QSMETHOD variable in QRS supplements and datasets, specifically the FTMETHOD, QSMETHOD and RSMETHOD variables in FT, QS and RS domains.
- The QRS Main page contains general information about the topic and is split into tabs for easy reference on various sub-topics: https://www.cdisc.org/standards/foundational/qrs
- The ‘QRS Naming Rules’ can be downloaded from the “QRS Resources” tab on the QRS Standards page: (you would need to log in to your CDISC account to access this link): https://www.cdisc.org/sites/default/files/2021-03/QRS_Naming_Rules_2021-03-05.xls
- The QRS Supplement request form – where sponsors can request new supplements to be added, by providing a reference paper as background information for the QRS instrument being requested: https://www.cdisc.org/sites/default/files/2020-11/CDISC_QRS_Supplement_Request_Form.docx
- The FACIT Item Bank: https://www.cdisc.org/sites/default/files/2020-11/FACIT_Item_Bank_QRS_Controlled_Terminology_2019-03-14_P37.xlsx
- The QRS Supplements lists which established questionnaires fall under what domain and provides a link to referenced documents and CRFs (if available). It would help understand what kind of rating scales or questionnaires fall under what domain: https://www.cdisc.org/public-review/qrs-supplements-0
- PANSS (Positive and Negative Syndrome Scale - used as an efficacy endpoint in clinical trials of acute schizophrenia to measure severity of psychopathology) - Clinical Classifications Supplement mapped to RS: https://www.cdisc.org/standards/foundational/qrs/positive-and-negative-syndrome-scale
- VIGNOS Rating Scale:
- AIMS: Clinical Classification mapped to RS (Clinician-rated scale to assess the severity of dyskinesias in patients taking neuroleptic medications):
  - https://wiki.cdisc.org/pages/viewpage.action?pageId=73145757
  - https://www.cdisc.org/standards/foundational/qrs/abnormal-involuntary-movement-scale

QRS SECTION LINKS AND REFERENCES:

- CDISC Wiki: QRS Sub-team: https://wiki.cdisc.org/display/QRSSUPP/SDS+QRS+Supplements+Home
- QRS Sub-team Charter on CDISC Wiki (you would need a separate account to the CDISC Wiki and access to the QRS sub-team space to access this link): https://wiki.cdisc.org/display/CDISCTC/Questionnaires%2C+Ratings+and+Scales+%28QRS%29+SubTeam+Charter
- CDISC Wiki: QRS Public Review: https://wiki.cdisc.org/display/QRSSUPP/Public+Review
- Muscular Dystrophy TAUG: https://www.cdisc.org/standards/therapeutic-areas/duchenne-muscular-dystrophy

ACKNOWLEDGMENTS

We’d like to extend our special thanks to David Neubauer at IQVIA, as well as Steve Kopko and Dana Booth from the CDISC SDS QRS sub-team for reviewing our paper and offering valuable input.
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