

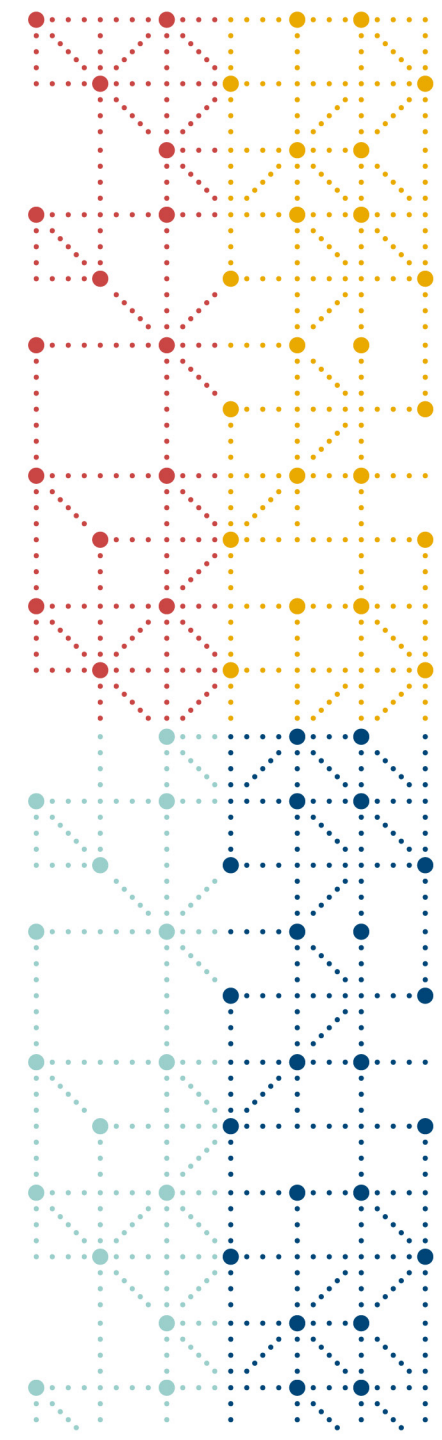
CDISC Doesn't Tell You What to Collect, But Regulators Do!

Presented by

Diane Wold
Sr. Director, Standards Development, CDISC

02.26.2019





Agenda

1. CDISC and FDA: Different kinds of advice
2. Data represented using CDISC standards
3. How to represent data in CDISC Standards
 1. CDISC sources
 2. FDA sources
4. Comparing CDISC and FDA Sources
5. Conclusion

CDISC and FDA: Different kinds of advice

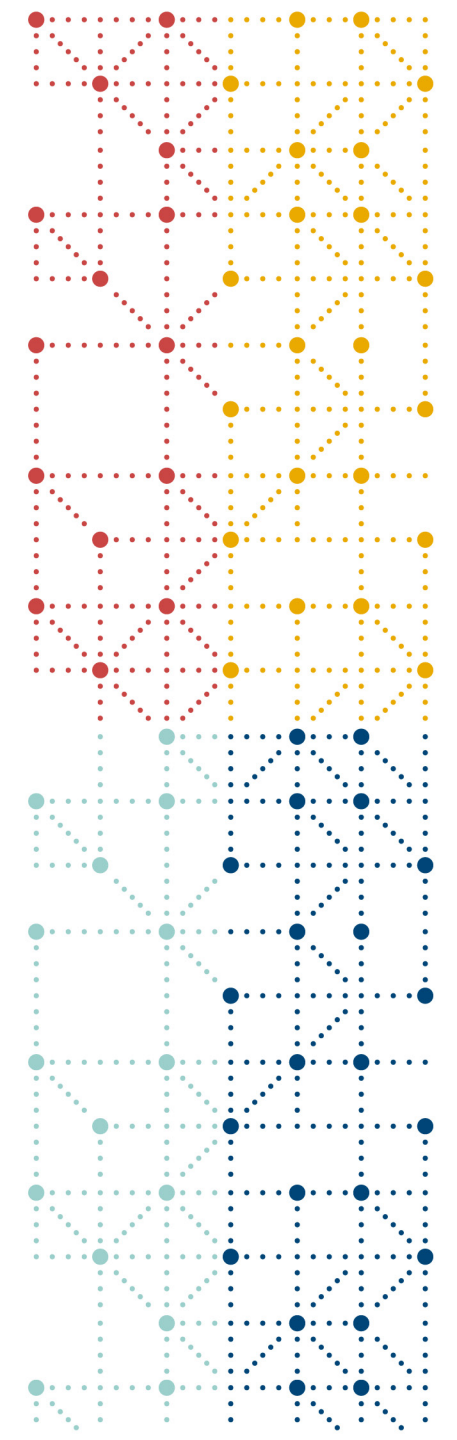


Remember...

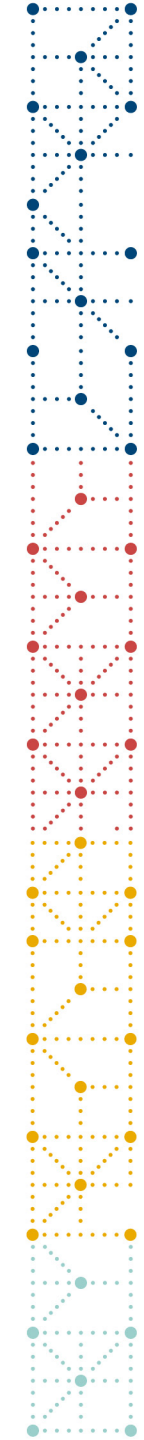
CDISC standards specify **how** to structure the data to support efficient data sharing for regulated clinical trials.

CDISC standards **do not** specify what data should be collected or how to conduct clinical trial protocols, assessments, or endpoints.

- What to collect is based on science.
- FDA guidances provide FDA thinking on that science.



Data represented using CDISC standards

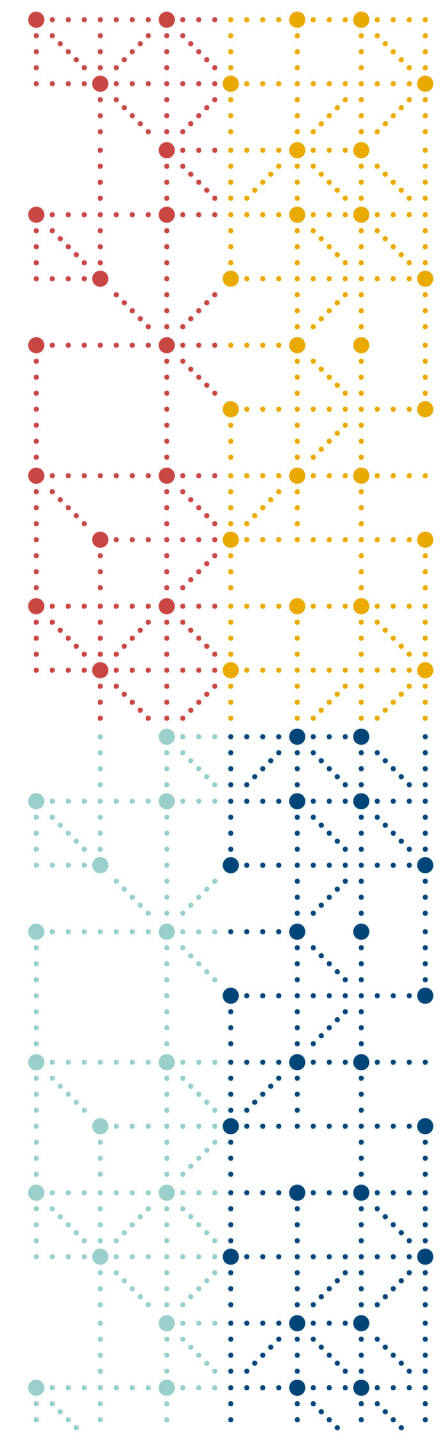


Not all data represented in CDISC standards is “collected”

- CDASH standards include “pre-specified” information in addition to data literally “collected” by filling in a form.
 - Header information
 - Information from question wording
- SDTM includes data from CDASH, plus derived data, mostly timing data
 - Study day variables, EPOCH variable
 - Subject Visits and Subject Elements datasets
 - Dates of study participation, study treatment, and death in Demographics
- ADaM includes data from SDTM but adds
 - Imputed values where collected values are missing
 - Derived variables (e.g., BASE, CHG, AVISIT)
 - Derived parameters

What variables should you include in submitted datasets?

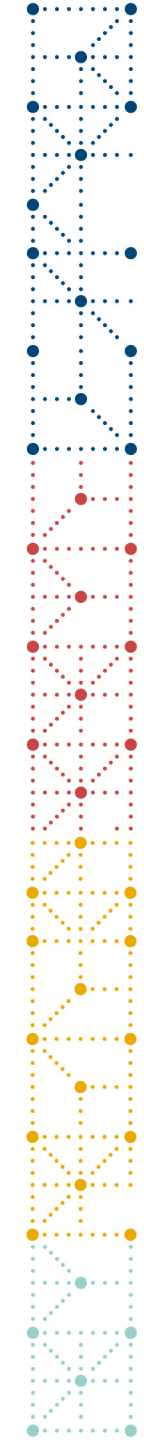
- CDISC standards indicate some required and expected variables.
- FDA TCG additionally requests study day variables and EPOCH in SDTM datasets.
- However, a variable that doesn't trace back to collected data or the study plans (protocol or SAP) can't be included.
- Examples in CDISC standards documents illustrate the standards, but are not normative. The inclusion of a particular variable or test in an example doesn't mean you have to collect it. It was included in the example to show how it could be represented **if** it was collected in a study. Whether to collect it is a study design decision.



How to Represent Data in CDISC Standards

CDISC sources

FDA sources



CDISC Sources

<https://www.cdisc.org/standards>

- Models (CDASH, SDTM, ADaM)
- Implementation Guides
- Conformance Rules
- Data Exchange Standards (ODM, Define-XML)
- QRS Supplements (for SDTM, and coming for ADaM)
- Therapeutic Area User Guides
- Controlled Terminology

- Normative content (in models, implementation guides, rules)
- Informative content (examples)

FDA Sources

- Technical Rejection Criteria are published in a separate FDA web page
<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM523539.pdf>
- The FDA Study Data Standards Resources page links to most of the important standards-related resources
<https://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>
 - Data Standards Catalog
 - Technical Conformance Guide
 - Business Rules
 - Technical Specifications
- A less-known resource has recommendations on LOINC
<https://www.fda.gov/downloads/forindustry/datastandards/studydatastandards/ucm586363.pdf>
- “Bioresearch Monitoring Technical Conformance Guide,” at
<https://www.fda.gov/downloads/drugs/developmentapprovalprocess/formssubmissionrequirements/ucm332468.pdf>
- “Bioresearch Monitoring Technical Conformance Guide,” at
<https://www.fda.gov/downloads/drugs/developmentapprovalprocess/formssubmissionrequirements/ucm332468.pdf>

How to structure data

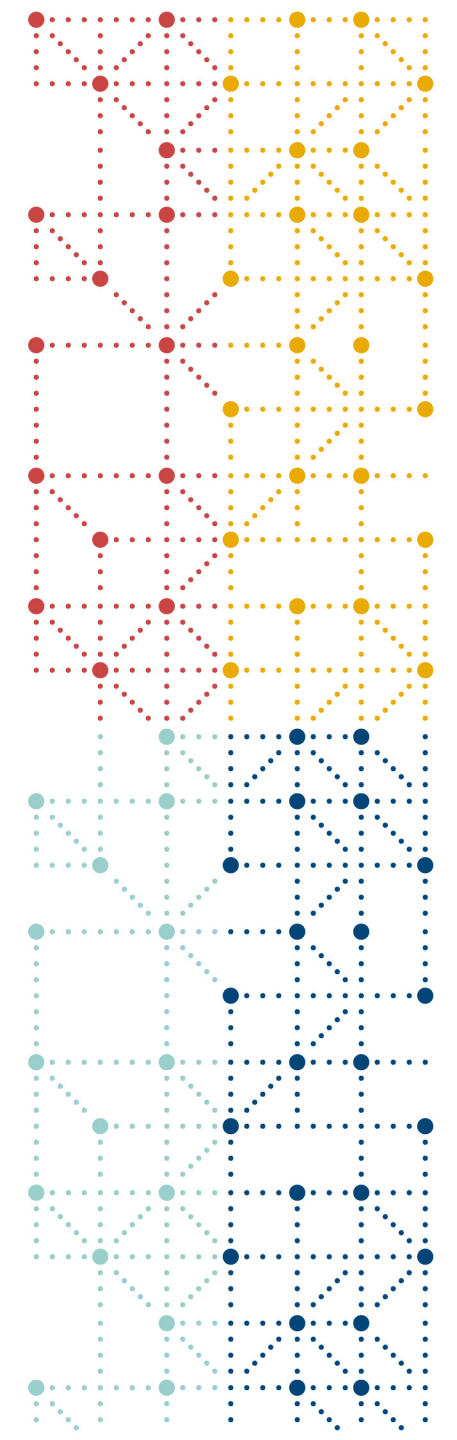


Remember...

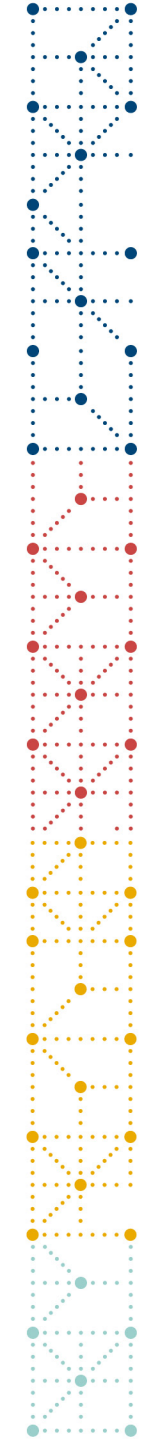
CDISC standards specify **how** to structure the data to support efficient data sharing for regulated clinical trials.

CDISC standards **do not** specify what data should be collected or how to conduct clinical trial protocols, assessments, or endpoints.

- FDA also specifies how to structure data
- By listing standards in the FDA Data Standards Catalog
 - Including SDTM, SEND, ADaM, Define-XML, CDISC Controlled Terminology
- By including additional requirements for how to structure data in other sources



Comparing CDISC and FDA Sources



FDA emphasis of CDISC requirements

- TCG Section 4.1.1.2 “Each individual subject should be assigned a single unique identifier across the entire application.”
- SDTMIG Section 4.2.3 “To identify a subject uniquely across all studies for all applications or submissions involving the product, a unique identifier (USUBJID) should be assigned and included in all datasets.”
- Business Rule FDAB020 “Demographics (DM) ... domain must be submitted.”
- SDTM Section 2.2.6 “Each study must include 1 standardized set of observations in a specific structure; this is the Demographics domain...”

FDA additions to CDISC requirements

- Data Standards Catalog: Terminologies such as MedDRA, WHODrug Global, and LOINC
- FDA TCG Section 4.1.4.1, “The variable EPOCH should be included for clinical subject-level observation...”
- FDA TCG Section 4.1.1.3, “The Subject Elements domain should be included...”
- FDA TCG Section 4.1.1.3, “Unless a simplified TS is indicated (see section 7.3), all TDM datasets should be included with each SDTM study submission to describe the planned conduct of a clinical study.”

Relationship between CDISC Requirements and FDA Requirements

- It would be nice if there were a clear division between CDISC and FDA requirements:



- However, CDISC standards include some FDA requirements
 - RACE code list
 - Trial Summary Parameter requirements

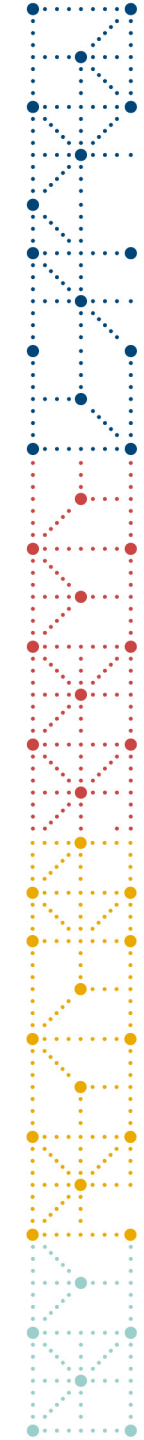


- And some FDA requirements conflict with CDISC requirements



Populating Arm Variables in Demographics

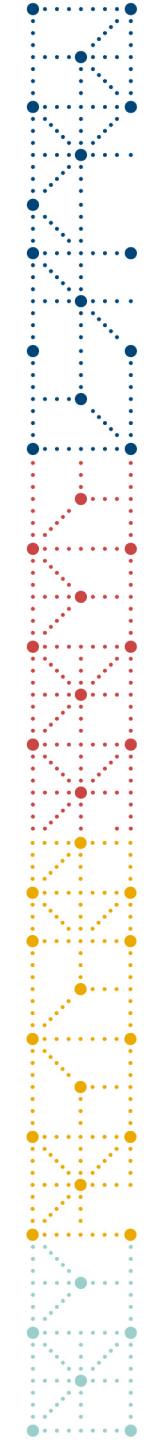
- SDTMIG v3.2 (and earlier) Demographics Domain assumptions describe special values for subjects who were screen failures, were not assigned to treatment or were not treated.
- FDA TCG Section 4.1.13 says that for such subjects the arm variables should be null. A footnote says, “Although this convention is inconsistent with the SDTMIG, FDA recommends its use so that ‘Screen Failure’, ‘Not assigned’, and ‘Not treated’ are not specified as a treatment arm.”
- SDTMIG v3.3 dropped the old special values and added two variables to deal with these cases.
- What does an implementer do in a submission based on a version of the SDTMIG before v3.3?



Arm Variable Workaround

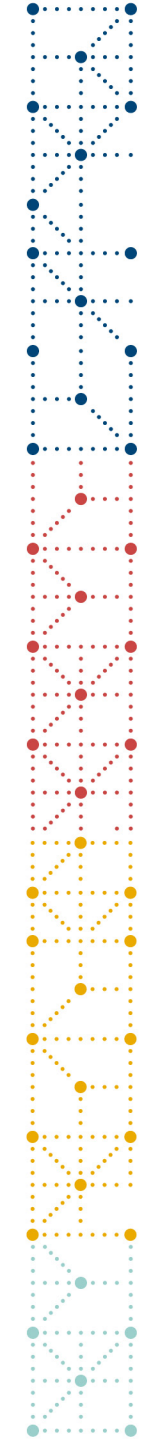
for submissions using a pre-SDTMIG v3.3 version of the standard

- One approach would be to add the new v3.3 DM variables as supplemental qualifiers, and follow the TCG convention for populating ARM, ARMCD, ACTARM, and ACTARMCD.
- Is this solution guaranteed to be acceptable to FDA?
- CDISC can't offer such a guarantee!
- My recommendation: Suggest an approach and ask the FDA whether they find it acceptable.
- Only FDA can say whether they would find an approach acceptable for a particular submission.



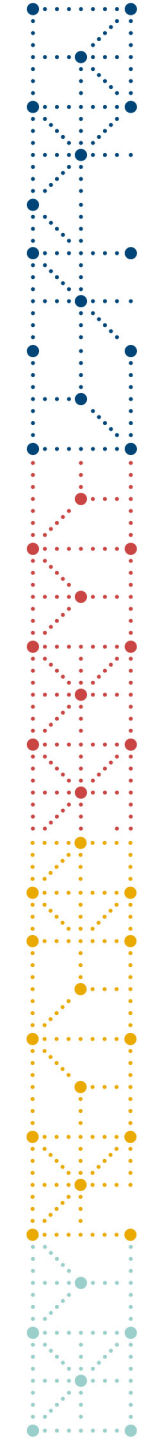
Populating AGE in Demographics

- Business Rule FDAB005: “Age or age range should be provided for all subjects, except for Screen Failures.”
- TCG Section 4.1.1.2, “No data should be imputed in SDTM datasets.”
- My company has interpreted data privacy regulations to mean that the company should collect year of birth, and not collect age.
- I am preparing a submission with trials that collected year of birth, but did not collect age. What do I do?



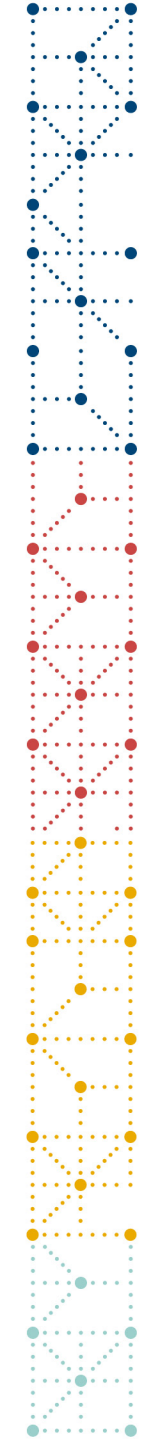
Workarounds when AGE was not collected

- One approach would be to populate AGE with an imputed value, document the imputation algorithm, and explain the approach in the Clinical Study Data Reviewers Guide (cSDG).
- Another approach would be to leave AGE null but provide an imputed age in a non-standard variable, document the imputation algorithm, and explain the approach in the cSDG. This would avoid the implication that AGE was collected.
- A third approach would be to leave AGE null and not provide an imputed age.
- Which approach would the FDA prefer? Ask them!



Workarounds when AGE was not collected

- One approach would be to populate AGE with an imputed value, document the imputation algorithm, and explain the approach in the Clinical Study Data Reviewers Guide (cSDRG).
- Another approach would be to leave AGE null but provide an imputed age in a non-standard variable, document the imputation algorithm, and explain the approach in the cSDRG.
 - This would avoid the implication that AGE was collected.
- A third approach would be to leave AGE null and not provide an imputed age.
- Which approach would the FDA prefer? Ask them!

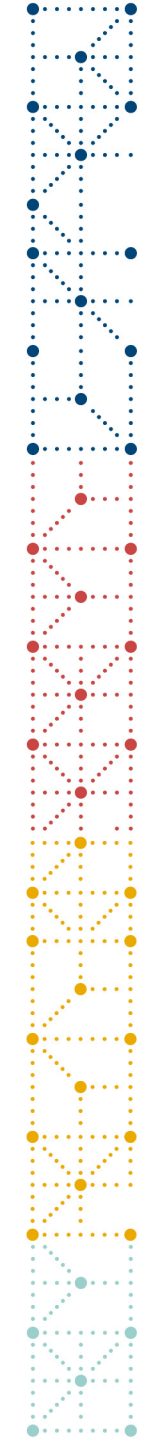


Subjects with Multiple Enrollments

- TCG Section 4.1.1.3:

“For subjects with multiple enrollments within a single study, the primary enrollment should be submitted in DM. Additional enrollments should be included in a custom domain with a similar structure to DM. Clarifying statements in the RG would be helpful.”

- SDTM-based custom domains must be based on one of the general observation classes, but DM is a special purpose domain.
- The advice in the TCG represents the direction CDISC is pursuing, but the draft standard is in an early stage of development, and is not complete or publicly available.
- I am preparing a submission with studies that include subjects with multiple enrollments. What do I do?
- Propose an approach to the FDA and ask them if it is acceptable!



Subjects with Multiple Enrollments

- TCG Section 4.1.1.3:

“For subjects with multiple enrollments within a single study, the primary enrollment should be submitted in DM. Additional enrollments should be included in a custom domain with a similar structure to DM. Clarifying statements in the RG would be helpful.”

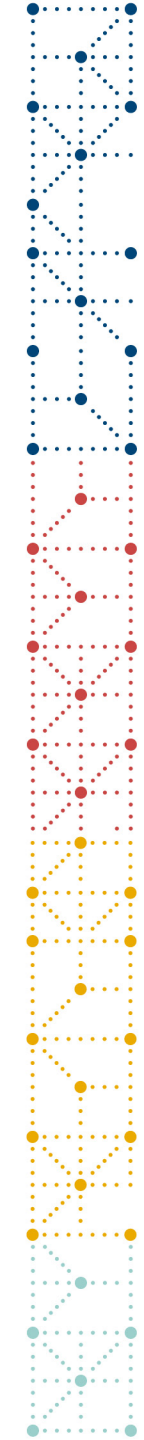
- SDTM-based custom domains must be based on one of the general observation classes, but DM is a special purpose domain.
- The advice in the TCG represents the direction CDISC is pursuing, but the draft standard is in an early stage of development, and is not complete or publicly available.
- I am preparing a submission with studies that include subjects with multiple enrollments. What do I do?
- Propose an approach to the FDA and ask them if it is acceptable!

Logically skipped questions in QS

- TCG Section 4.1.1.3 advice on the QS domain notes that “Some items in an instrument may be logically skipped per the instrument’s instructions.”
- The TCG provides details on how the FDA would like logically skipped questions represented.
- If the instrument includes instructions for scoring logically skipped questions, FDA advice includes populating STAT with “NOT DONE” while also populating the result variables, including QSORRES, as described in those instructions.
- Many implementers have not included records for logically skipped questions in SDTM datasets.
- The SDTMIG says that –ORRES should be null when STAT is “NOT DONE”

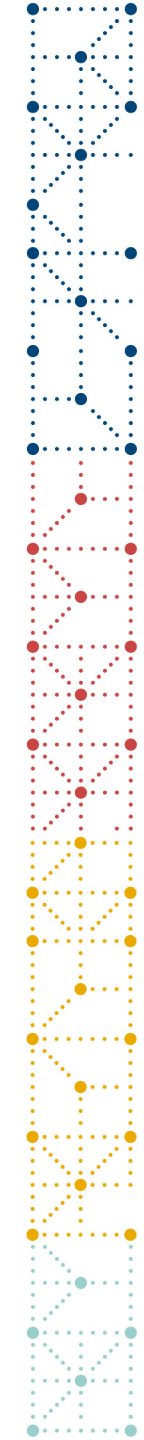
Logically skipped questions in QS

- TCG Section 4.1.1.3 advice on the QS domain notes that “Some items in an instrument may be logically skipped per the instrument’s instructions.”
- The TCG provides details on how the FDA would like logically skipped questions represented.
- If the instrument includes instructions for scoring logically skipped questions, FDA advice includes populating STAT with “NOT DONE” while also populating the result variables, including QSORRES, as described in those instructions.
- Many implementers have not included records for logically skipped questions in SDTM datasets.
- The SDTMIG says that –ORRES should be null when STAT is “NOT DONE”



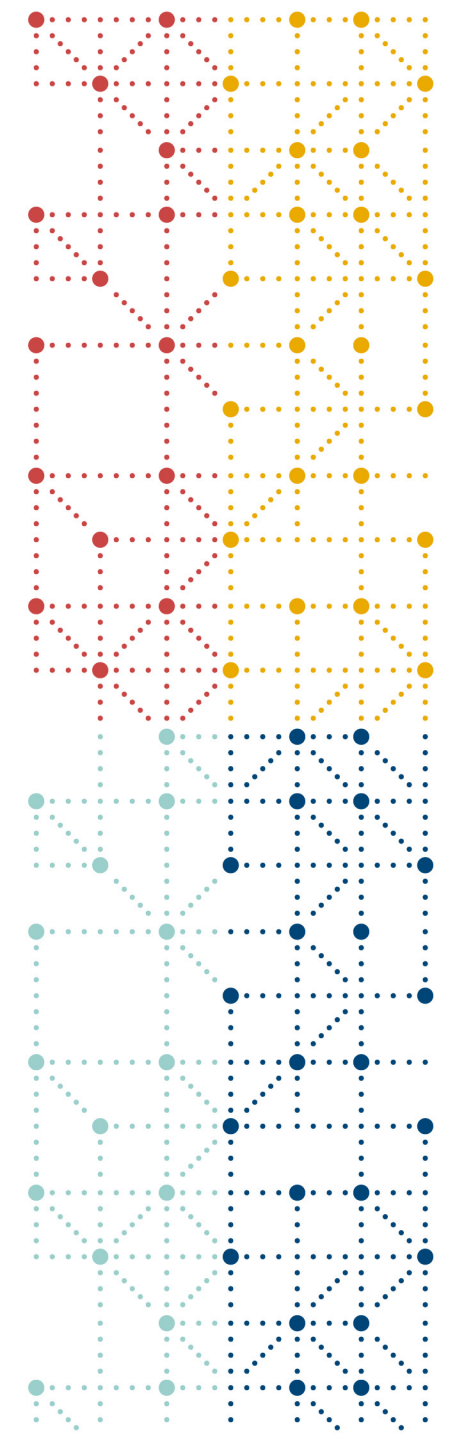
Handling Logically Skipped Questions

- CDISC is committed to developing help for implementers who need to comply with FDA requirements for logically skipped questions, but this help is not complete or publically available.
- I am preparing a submission which includes questionnaires with logically skipped questions. What do I do?
- Propose an approach to the FDA and ask them if it is acceptable!

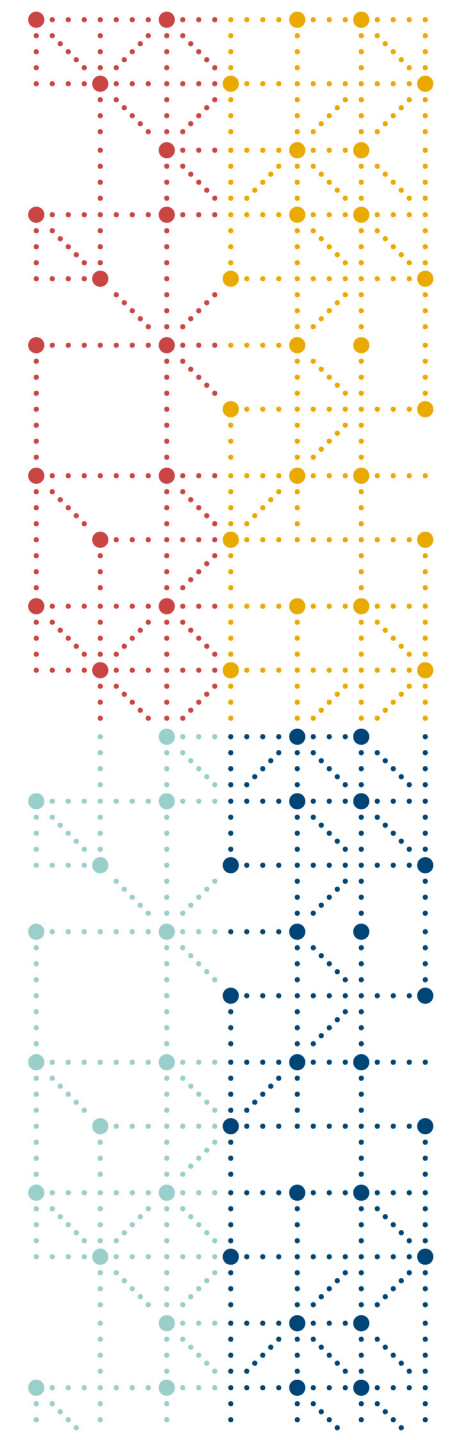


Handling Logically Skipped Questions

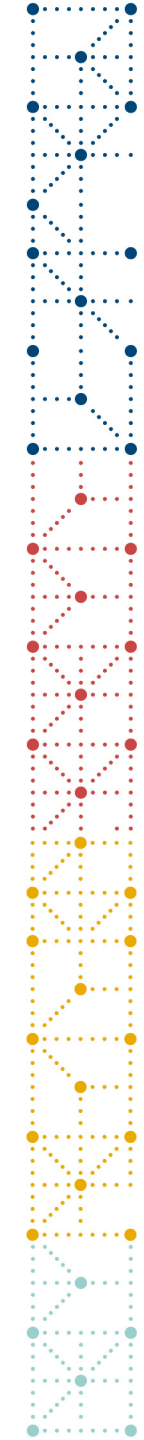
- CDISC is committed to developing help for implementers who need to comply with FDA requirements for logically skipped questions, but this help is not complete or publicly available.
- I am preparing a submission which includes questionnaires with logically skipped questions. What do I do?
- Propose an approach to the FDA and ask them if it is acceptable!



Conclusion

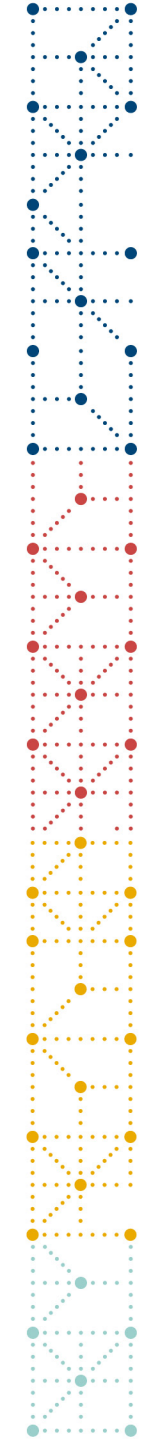


Conclusion



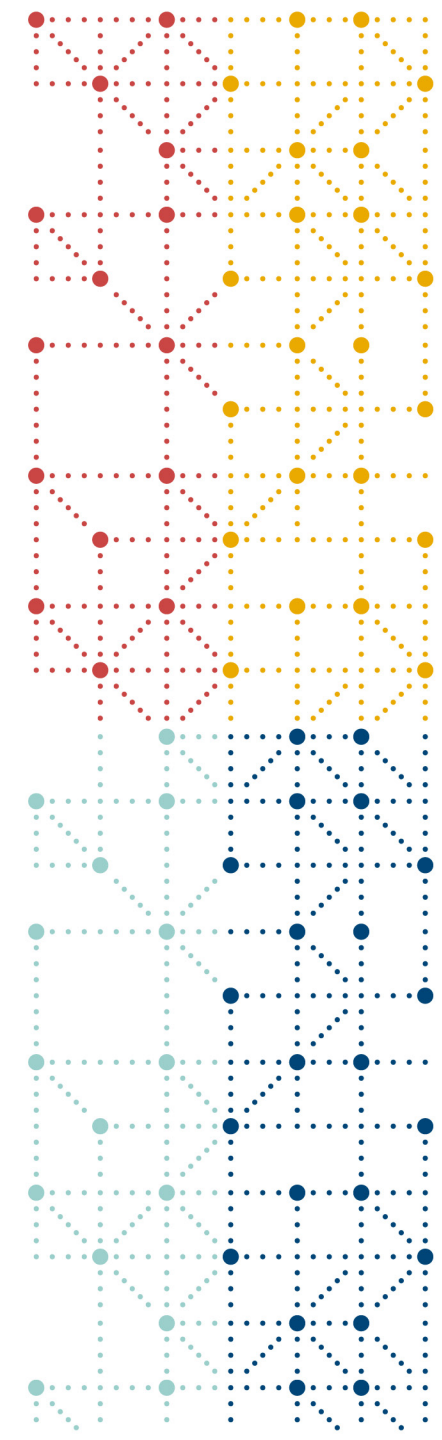
Conclusion

- CDISC doesn't tell you what data to collect.
- CDISC alone doesn't tell you everything you need to know for a regulatory submission. You also need to consult regulatory sources.
- Most regulatory requirements reiterate or add to CDISC requirements.
- Some regulatory requirements conflict with CDISC requirements.
 - Some conflicts can be resolved with fairly straight forward workarounds.
 - Other conflicts are more difficult to resolve.
- What do I do when faced with a conflict between CDISC and regulatory requirements?
- Propose an approach to the regulator and ask if it is acceptable to them!



Conclusion

- CDISC doesn't tell you what data to collect.
- CDISC alone doesn't tell you everything you need to know for a regulatory submission. You also need to consult regulatory sources.
- Most regulatory requirements reiterate or add to CDISC requirements.
- Some regulatory requirements conflict with CDISC requirements.
 - Some conflicts can be resolved with fairly straight forward workarounds.
 - Other conflicts are more difficult to resolve.
- What do I do when faced with a conflict between CDISC and regulatory requirements?
- Propose an approach to the regulator and ask if it is acceptable to them!



Thank You!

Diane Wold

diane.wold@cdisc.org

