cdisc

2023
US
INTERCHANGE

FALLS CHURCH, VA | 18-19 OCTOBER

Conformance Rules
CDISC Open Rules Engine

Presented by Peter Van Reusel, Chief Standards Officer, CDISC
Amy Palmer, Head of Standards Operations, CDISC

Meet the Speakers

Peter Van Reusel

Title: Chief Standards Officer

Organization: CDISC

Peter Van Reusel provides executive leadership to the development and implementation of clinical standards in line with CDISC's strategy and operational plans, working closely with the President and CEO, as well as CDISC staff and stakeholders. He has over 20 years' experience in senior roles in pharma and at CROs, providing standards expertise and carrying out other standards work in various organizational settings.

Amy Palmer

Title: Head of Standards Operations

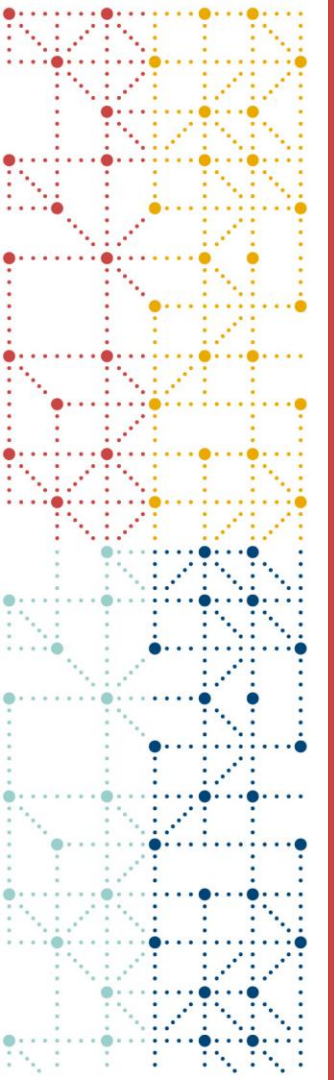
Organization: CDISC

Amy has been with CDISC since 2013. She is a member of the CDISC Technical Leadership Team and leads the Global Governance Group. Amy has over 28 years' experience working in clinical research. She has been involved in the development of multiple therapeutic area user guides as well the foundational standards and has been working with CDISC standards since 2010.

Conformance Rules
CDISC Open Rules Engine

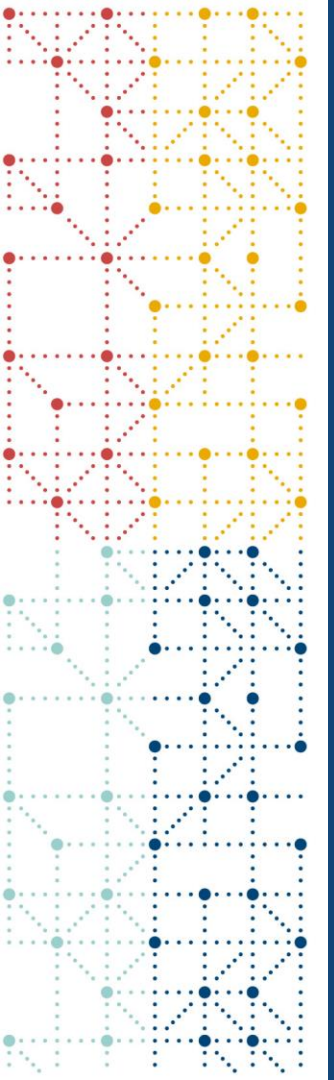
Peter Van Reusel, Chief Standards Officer

CDISC



Agenda

- CORE Concept
- Conformance Rules
- Rules Governance Model
- CORE Engine and Deployments
- What's Next



CORE Concept

The Challenge

A single source of truth for all conformance rules

Consistency across conformance rule implementations

Central management and governance of rule specifications, regardless of source:

- CDISC – rules in the foundational standards
- FDA Validator Rules
- PMDA Validation Rules
- Community – proposed new/updated rules

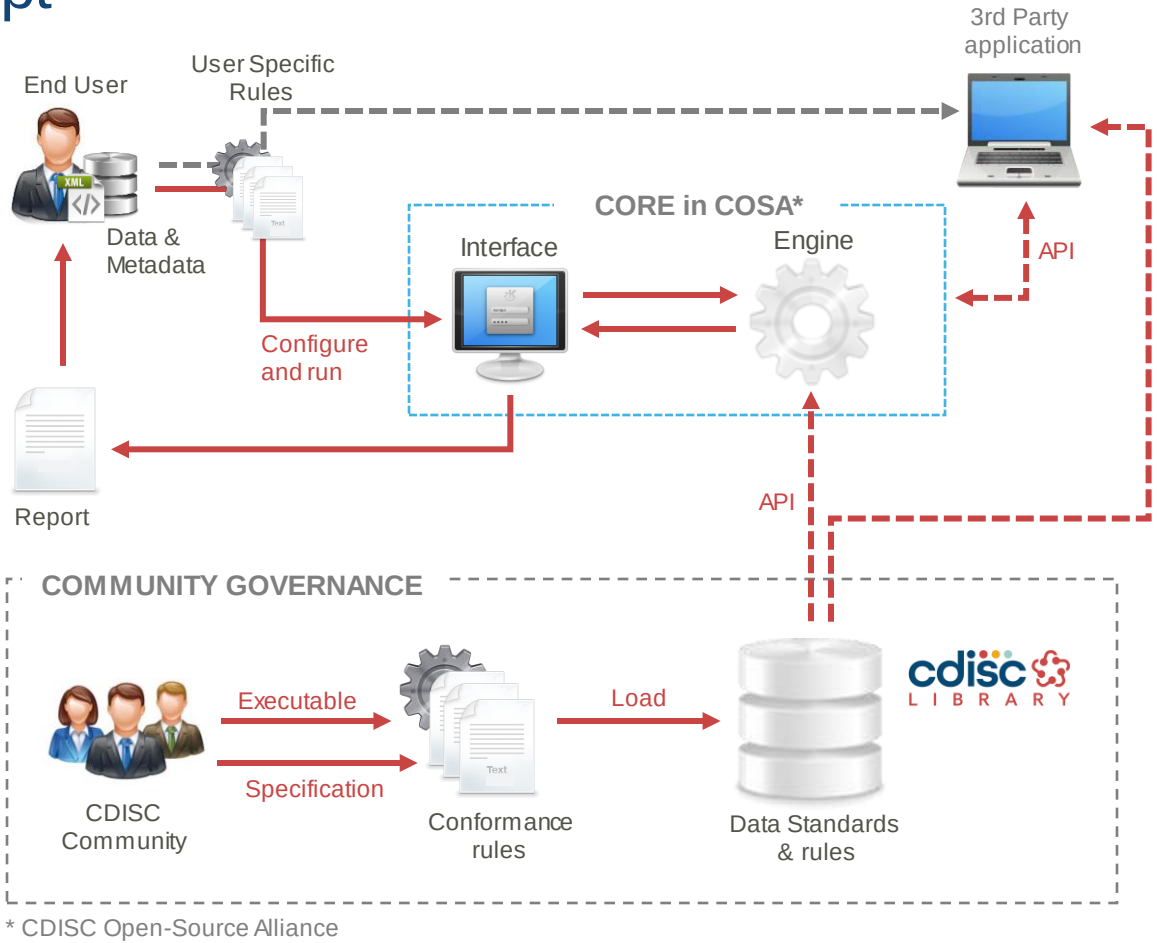
Development, central management and governance of machine-executable rules from specifications

Efficient and transparent process for the community to

- Access specifications
- Access executable rules
- Propose new/updated rules

cdisc

CORE Concept



Conformance Rules

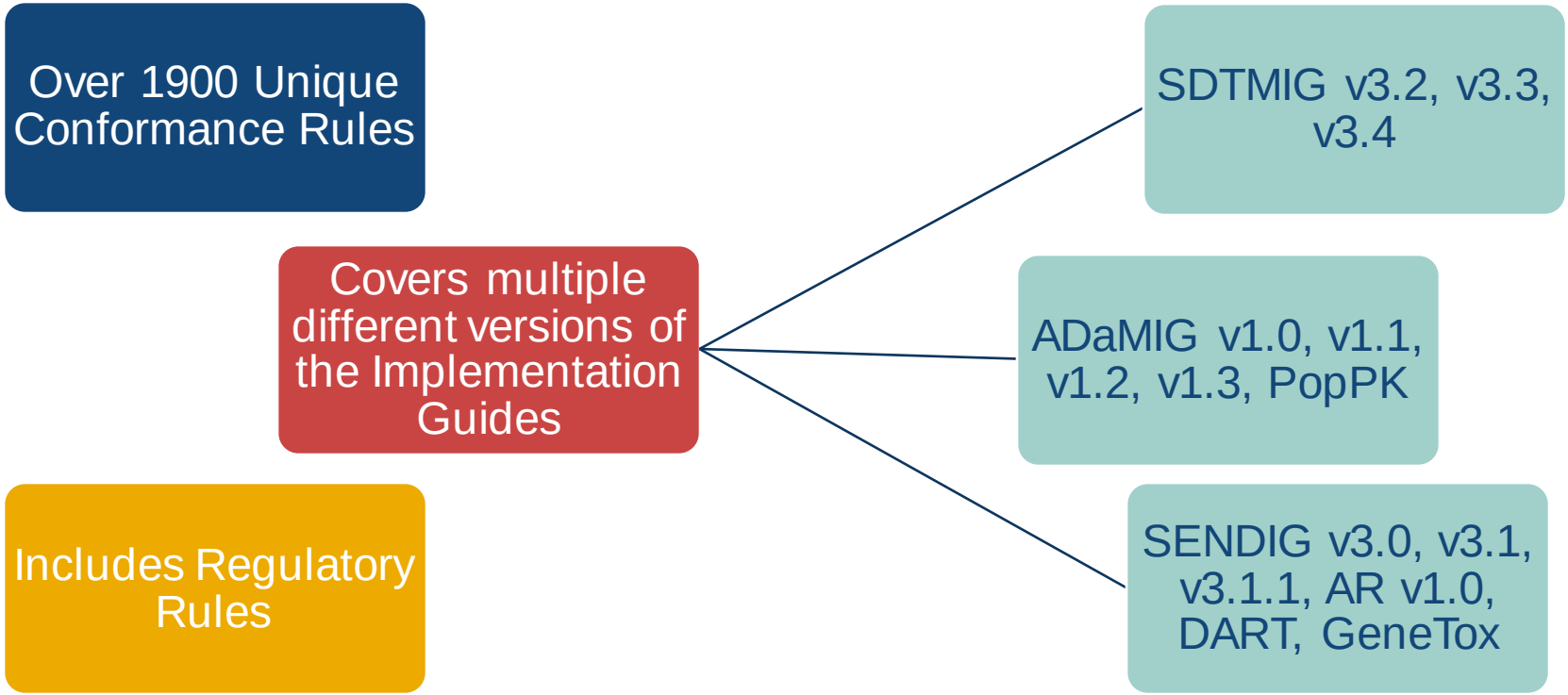
EDIT TEST DIFF

```yaml
# Variable: EXMETHOD
# Condition:
# Rule: EXMETHOD not present in dataset
Authorities:
  - Organization: CDISC
    Standards:
      - Name: SDTMIG
        References:
          - Citations:
              - Cited Guidance: Method of administration of the treatment. Not to be used with
                  human clinical trials.
                Document: Model v1.7
                Item: EXMETHOD
                Section: Table 2.2.12.1
            Origin: SDTM and SDTMIG Conformance Rules
            Rule Identifier:
              Id: CG0568
              Version: '1'
            Version: '2.0'
        Version: '3.3'
Check:
  all:
    - name: EXMETHOD
      operator: exists
Core:
  Id: CORE-000326
  Status: Published
  Version: '1'
Description: Trigger error when EXMETHOD exists in the EX dataset for human clinical trials
Executability: Fully Executable
Outcome:
  Message: EXMETHOD is not to be used with human clinical trials
Rule Type: Record Data
Scope:
  Classes:
    Include:
      - INTERVENTIONS
  Domains:
    Include:
      - EX
Sensitivity: Record
```

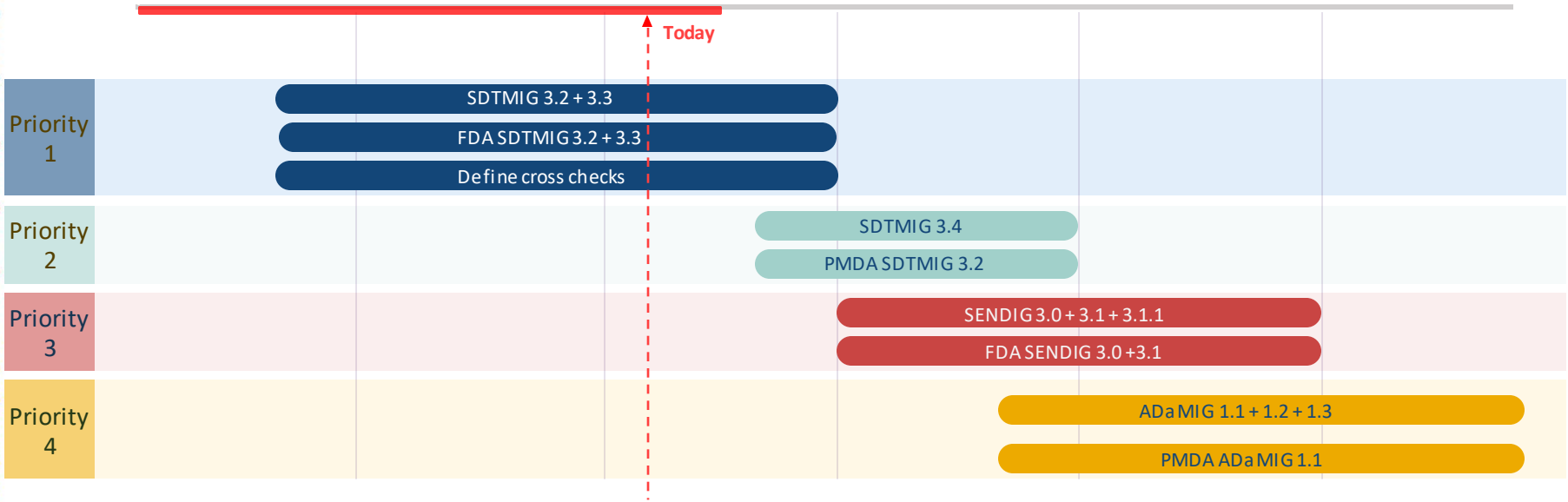
CORE Rule Editor

- Web-based application, no software to install
- Structured document, 1 CORE rule per file containing rule's metadata & check logic
- Real-time syntax checking

Volume and Breadth of Conformance Rules



Rules Development Priority



➡ *Timelines depend on community engagement*

Rules Governance Model

CORE Rules Governance

Rules Governance Team
(CDISC; Regulatory Agencies; Community)

Rule Specifications

CORE Rules (executable)

cdisc Standards

Provide rule specs

Regulatory Agencies

Provide validation rules

Community

Propose new / updated rule specs

Rules Gov Team Activities
- Receive specifications
- Load to central catalog

Rules Gov Team Activities
- Govern specs content
- Curate content
- Mark rules for dev.
- Prioritize rules for dev.

Central Specifications Catalog

Freely Available

Rules Gov Team Activities
- Govern CORE Rules dev. process
- Assign Rules for development
- Review /approve Rules for release

Rules Development

Community

Publish

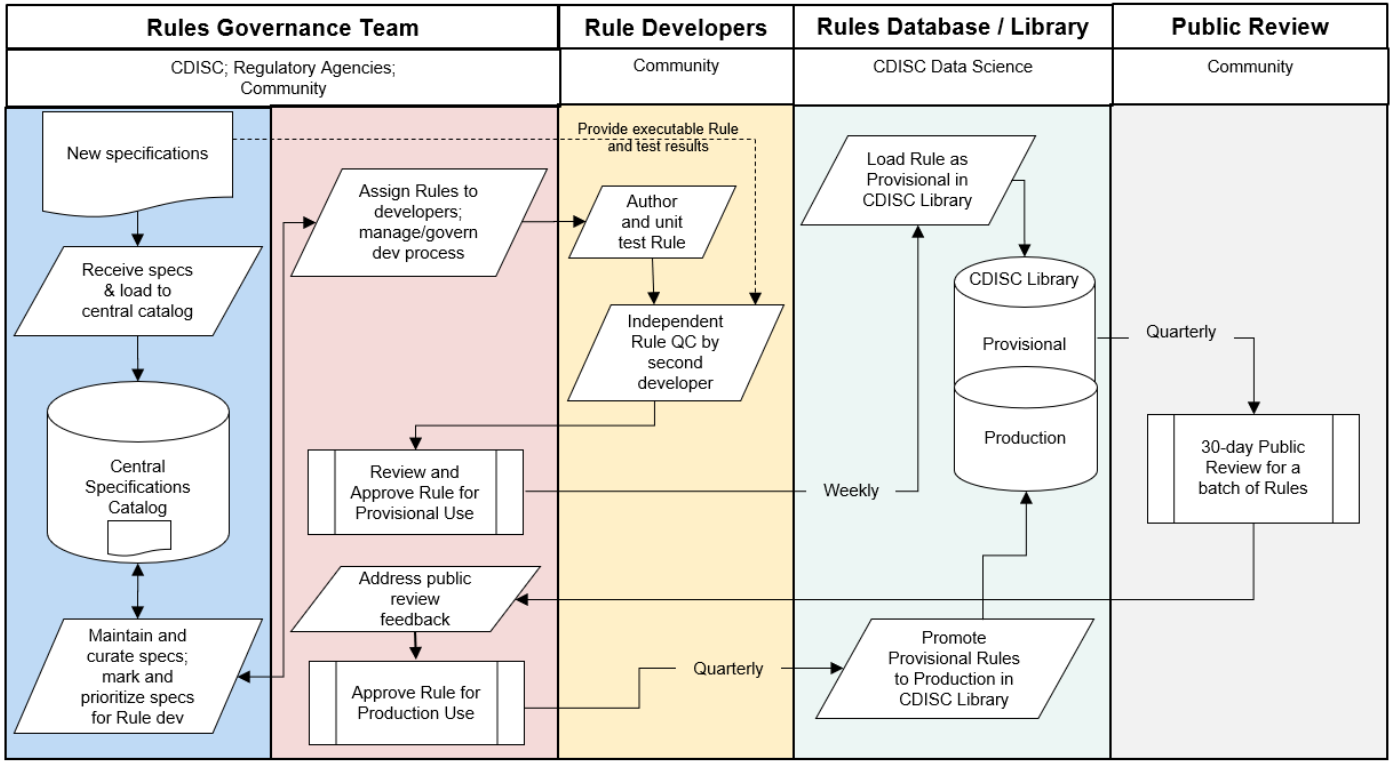
CDISC Library

API

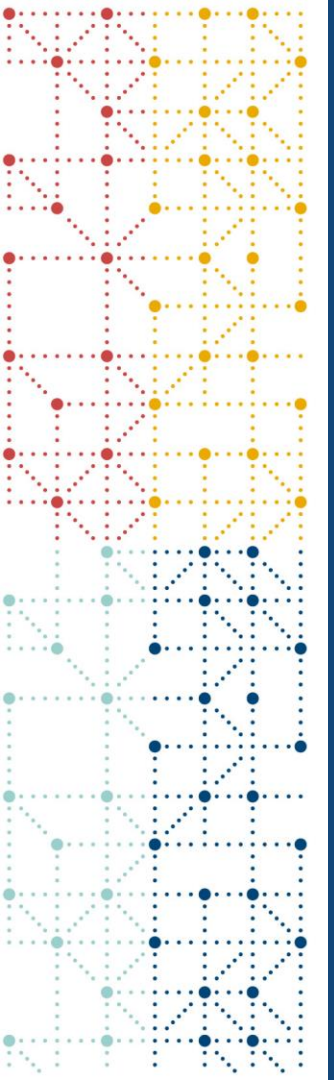
3rd Party Applications

CORE Engine

Conformance Rules: Governed Development Process



➡ *Governance model is complete; implementation is in progress*



CORE Engine and Deployments

CORE Engine and Rule Editor are Open-Source

- Open-source framework
  - Listed in the COSA (CDISC Open-Source Alliance) directory
  - Permissive MIT open-source license
  - Provided via GitHub
- Free to all in CDISC community
- Very flexible implementation options

cdisc

Third-party Desktop Deployments

- Early discussions with vendor community re early provision of standalone CORE Engine desktop version
  - Simple to install and use
  - Provide a UI
  - Will make it easier for the CDISC community to evaluate CORE without IT support

- First free, publicly available, vendor-provided CORE desktop version announced at the CDISC European Interchange

- CORE is a Reference Implementation
  - The principle is commonly used in the software industry
  - Provides a concrete example on how the standard should be implemented

➡ *Drive adoption*

cdisc

CORE Registered Solution Provider

- Program purpose
  - For CORE vendors (solution providers)
    - Certify with CDISC that their solutions correctly use the Conformance Rules
  - For CDISC
    - Treat all CORE vendors equally
    - Achieve a level playing field regarding use of any Engine with the Conformance Rules
    - Inform the community which solutions have been certified

- Testing for certification will include
  - Generating results with Conformance Rules and test study data reflecting an “average study”
  - No system functionality testing

cdisc

What’s Next

Adoption by Regulatory Agencies

- One version of the truth will benefit the regulatory submission ecosystem
- CDISC and FDA are discussing joint governance and publication of rule specifications
- Single version of rule specifications followed by single version of executable rules implementation

A future where regulatory agencies use CORE Rules

Adoption by Industry

- TransCelerate Digital Data Flow
  - Conformance Rule Proof of Concept on Unified Study Definition Model (USDM)
- Tobacco Implementation Guide
  - Creating new TIG-specific rules
  - Aligning with existing conformance rules
- Various Implementations with Vendors, Sponsors, and CROs

Moving forward with additional implementations

Next Milestone

- The complete ruleset for
  - SDTM 3.2 and SDTM 3.3
  - Define.xml crosscheck rules
  - FDA validator rules v1.6 (that apply to SDTM 3.2 and SDTM 3.3)
  - FDA Technical Rejection Criteria

- CORE Engine Stable Release
  - Engine can run all the rulesets above
  - Thorough testing and validation documentation

- Purpose
  - Test with real study data and roll out rules governance process

Implementers can integrate this stable version
Drive adoption and test with real study data

In Summary

- Rules
  - Full set of executable rules for submission standards (SDTM, SDTMIG, SENDIG, ADaMIG)
  - Including Regulatory-specific rules
  - Including Define.xml cross-check rules

  ➔*Continuing volunteer engagement is critical!*

- CORE is the Reference Engine
  - Engine with all basic functionality for full set of machine-executable rules
  - Includes a validation package

- CDISC will establish a CORE certification program
  - To verify output of different applications versus the CORE Reference Engine
  - CDISC conformance rules are the single version of the truth

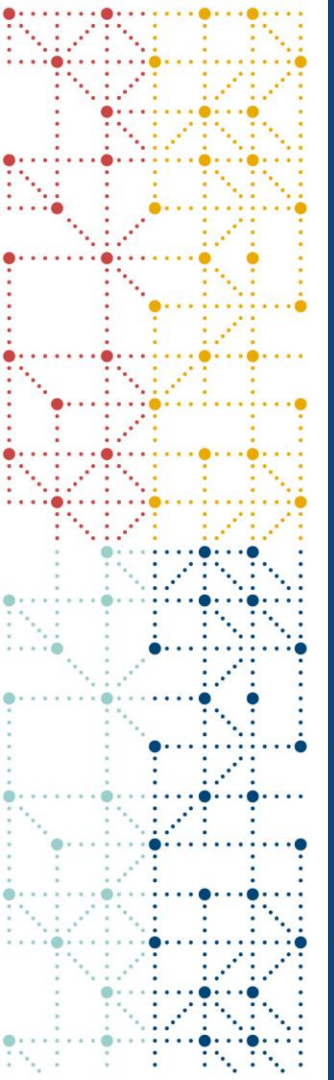
Rules are part of the Standards!
Expect Regulatory Agencies to mandate use of CDISC Conformance Rules

Rules Development

Amy Palmer, CDISC

Agenda

- Developing Rules
- From Rule Specifications to a CORE Rule
- Writing Conformance Rules with CORE in Mind
- What's Next for CORE
- How Can You Help?



Developing Rules

Conformance Rule Specifications and CORE Rules

Rule Specifications

- Human-readable
- Sources:
  - Typically, a part of CDISC Foundational Standards (developed per COP-001)
  - Alternately, Regulatory-provided rules
  - In the future, community-provided data quality rules or traceability rules

CORE Rules

- Machine-executable
- Re-expression of conformance rule specifications in machine-executable form
- Developed by the CDISC Community

From Rule Specifications to a CORE Rule

Where Do These Conformance Rules Come From?

- An **Expected** variable is any variable necessary to make a record useful in the context of a specific domain. Expected variables may contain some null values, but in most cases will not contain null values for every record. When the study does not include the data item for an expected variable, however, a null column must still be included in the dataset, and a comment must be included in the Define-XML document to state that the study does not include the data item.

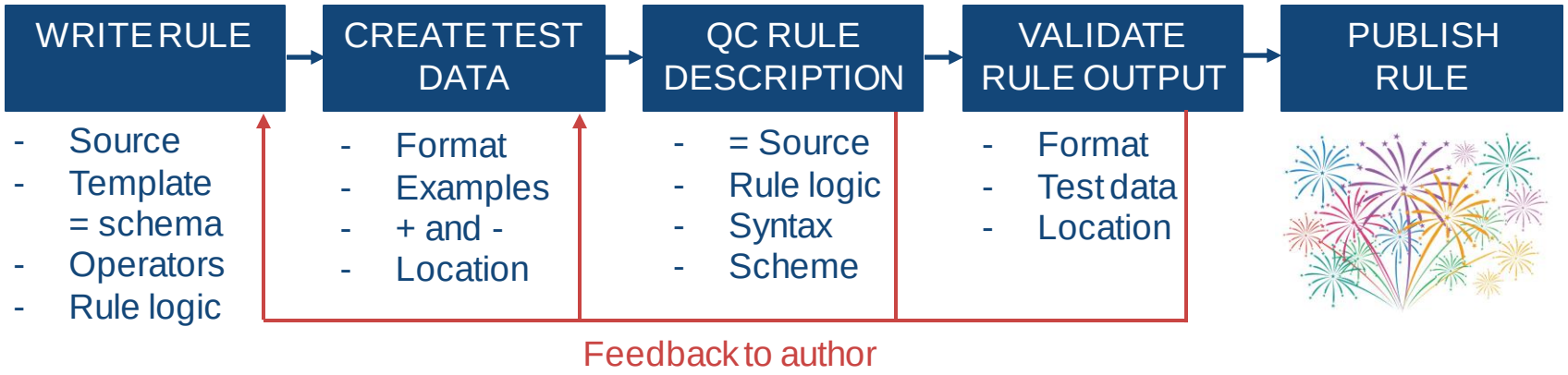
	Rule ID	SDTMIG Version	Rule Version	Class	Domain	Variable	Condition	Rule
38	CG0016	3.2	1	ALL	ALL	GEN	Variable Core Status = Expected	Variable present in dataset
39	CG0016	3.3	1	ALL	ALL	GEN	Variable Core Status = Expected	Variable present in dataset
40	CG0016	3.4	1	ALL	ALL	GEN	Variable Core Status = Expected	Variable present in dataset

Regulatory Rules

version 1.6, finalized December 2022

FDA Validator Rule ID	Publisher	Publisher ID	FDA Validator Rule Message	FDA Validator Rule Description
SD1137	CDISC	CG0348	Non-missing value for --ORRES, when --DRVFL='Y'	Character Result/Finding in Original Units (--ORRES) value should be NULL, when Derived Flag (--DRVFL) value is 'Y'.
SD1235	CDISC	CG0554	Neither SPDEVID nor USUBJID values are populated	Value for Sponsor Device Identifier (SPDEVID) or Unique Subject Identifier (USUBJID) variables should be populated for all records in Divice In-Use (DU) domain
SD9999	CDISC	CG0320, CG0321, CG0463, CG0464, 266, 266.1, 267, 267.1, 268, 268.1, 269, 269.1	Dataset class not recognized	The structure for custom dataset should be based on one of the general observation classes (EVENTS, FINDINGS, INTERVENTIONS) defined by the SDTM model.
SD1075	CDISC	CG0467, 78	Variable not recommended for use	Variables described in IG as not recommended for usage should be not included in the dataset.

CORE Rules Process



* Developing and Implementing CDISC CORE: a Data Managers Testimonial, Els Janssens, CDISC EU Interchange

HardCORE Practice

Source = SDTM and SDTMIG Conformance Rules v2.0

Rule ID	SDTMIG Version	Rule Version	Class	Domain	Variable	Condition	Rule
CG0032	3.4	2	ALL	ALL	VISITDY	VISITNUM is in TV.VISITNUM	VISITDY = TV.VISITDY

```yaml
Check:
  all:
    - name: VISITDY
      operator: exists
    - name: VISITNUM
      operator: is_contained_by
      value: $tv_visitnum
    - name: VISITDY
      operator: not_equal_to
      value: TV.VISITDY
Match Datasets:
  - Name: TV
    Keys:
      - VISITNUM
Core:
  Id: CORE-000249
  Version: '1'
  Status: Published
Description: Verify that visitdy is planned and exists in TV
Operations:
```

```yaml
Operations:
  - domain: TV
    id: $tv_visitnum
    name: VISITNUM
    operator: distinct
Outcome:
  Message: Visit Day cannot be found in Trial Visit (TV) domain
  Output Variables:
    - VISITDY
    - VISITNUM
Rule Type: Record Data
Sensitivity: Record
```

```
Check:
Missing property "Executability". ya
```

Automatic detection of errors

HardCORE Practice

Validation in Rule Editor

Does everything work?

EDIT TEST

- Validate YAML Syntax
- Validate YAML against Schema
- Convert YAML to JSON Rule
- Load Test Data
- Results

Loading test data

Load Test Data

TEST DATASETS FILE...

Filename: unit-test-coreid-CG0513-negative 1.xlsx

Check output - expected?

Results Negatives 4

Results


```
{ 1 item
  "DM" : [ 1 item
    0 : { 5 items
      "executionStatus" : "success"
      "domain" : "DM"
      "variables" : [ 2 items
        0 : "ACTARMCD"
        1 : "ARMNRS"
      ]
      "message" : "ACTARMCD is empty, but ARMNRS is not completed."
      "errors" : [ 4 items
        0 : { 3 items
          "value" : { 2 items
            "ACTARMCD" : ""
            "ARMNRS" : ""
          }
          "row" : 4
          "uSubjId" : "CDISC004"
```

Developing CORE Rules in the Future

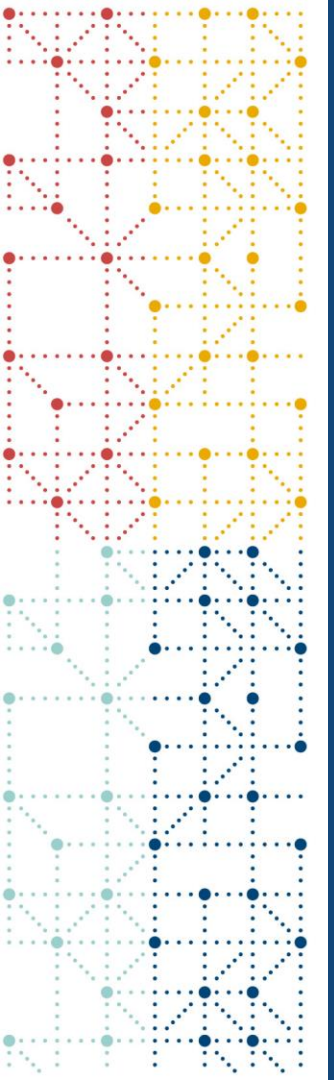
Plan to draft the rule logic within the CORE Rules Editor

Use the Rule Description and Outcome Message to review rule during Internal and Public Review

Cited Guidance is part of the Rule

Rule Logic is transparent

cdisc



Writing Conformance Rules with CORE in Mind

Conformance Rules Intent and Meaning

- Some rules are ambiguous?
- What does the standard say?
- Did the authors really mean to say this?

Rule Writing Best Practices

Write	Write rules with the Rule Editor in mind
Use	Use logic to draft rules
Clear	Clear, concise, unambiguous language in the Implementation Guides and Models
Limit	Limit words like “should” and “may” in cited guided intended for conformance rules

What’s Next for CORE

Future Applications of Checks in CORE

Therapeutic Area-Specific Checks

Data Quality Checks

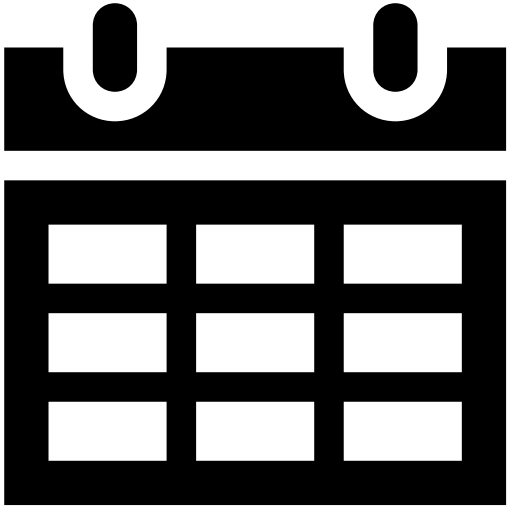
Therapeutic Area-Specific Checks

For Example:

In a prostate cancer trial, would expect all participants to have SEX = M in the DM dataset

```yaml
all:
    - name: SEX
      operator: not_equal_to
      value: M
    - name: SEX
      operator: non_empty
```

Data Quality Check



For Example:

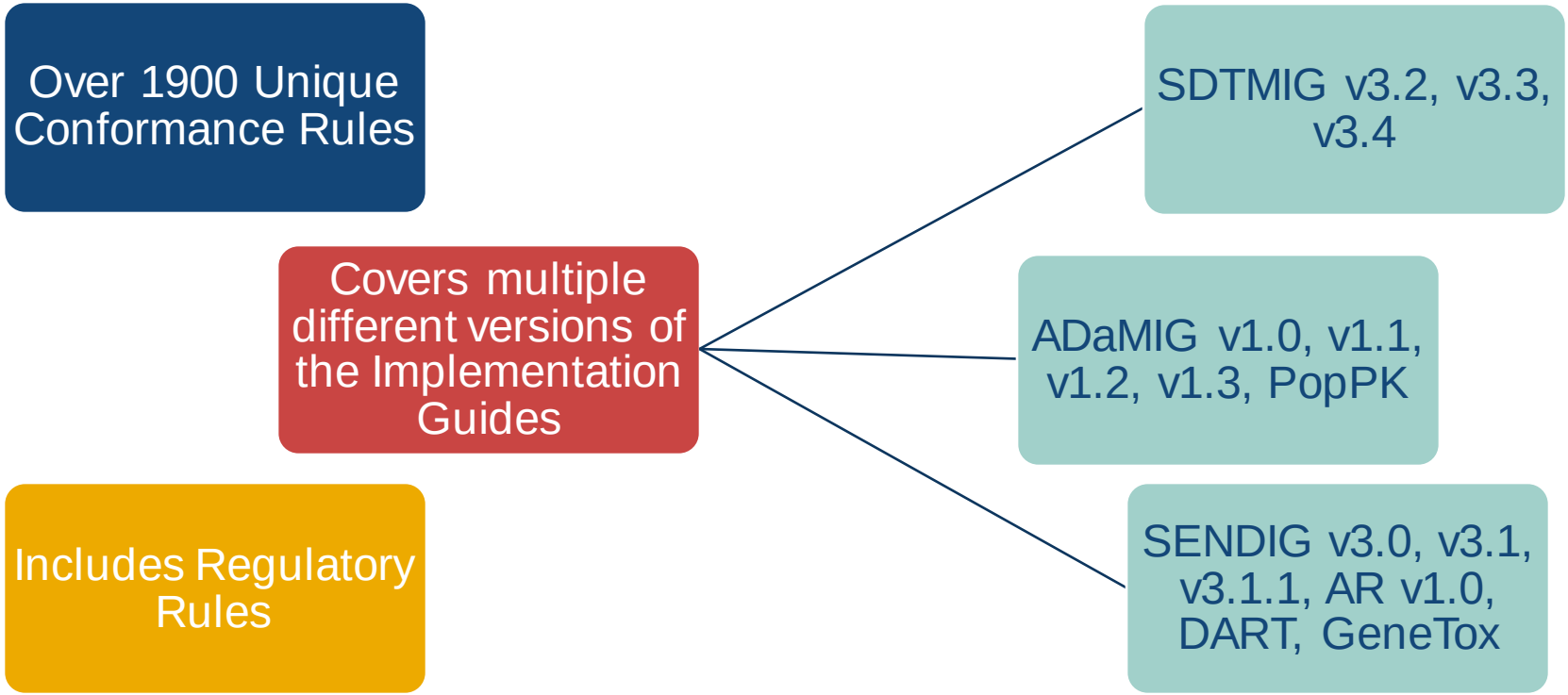
The AE Start Date must be earlier than AE End Date

```
Check:
  all:
  -       name: AESTDTC
          operator:date_greater_than_or_equal_to
          value: AEENDTC
```

Remember: Rule logic is written as failure criteria!

How Can You Help?
We Can’t Do This Without You

Volume and Breadth of Conformance Rules



Benefits of Volunteering

Training on the CORE Rule Editor

Meet with experts to ask your rule drafting questions

Increase your Knowledge

Develop a clearer understanding of the CDISC standards

Learn how to use CORE to develop study-specific rules and data quality checks

Recognition of individuals and their organizations for ongoing volunteer support for CORE project on the CDISC Website

How to Volunteer

- https://www.cdisc.org/volunteer/form
  - Select CORE Rules Team

Expected Engagement

- Time Period: 3 - 6 months, or longer, if able
- Hours per week: 2 - 4 hours, in addition to meeting attendance
- Weekly Meetings and Workshops: Recorded and available for review
  - Rules Development Workshop Tuesdays 9:30am - 11am ET
  - Weekly Team Meeting – Thursdays 11am - 12pm ET

Session 6C – CORE Workshop

Gerry Campion and Amy Palmer, CDISC

Multiple Exercises using the CORE Rule Editor

- SDTMIG Rule
- Therapeutic Area/Study-specific Rules
- Data Quality Checks
- FDA Technical Rejection Criteria

Remember to bring your laptop!

Relentless Collaboration

Thank You!

pvanreusel@cdisc.org

apalmer@cdisc.org