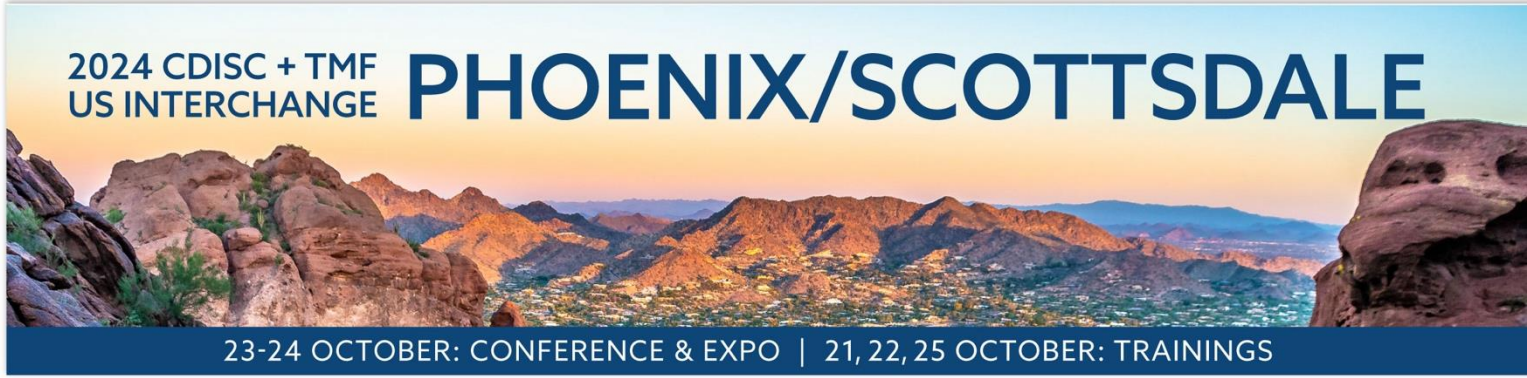


FDA business rules and CDISC Open Rules, the road to adoption

Nick De Donder, CDISC Open Rules Program Manager, CDISC

Meet the Speaker

Nick De Donder

Title: CDISC Open Rules Program Manager

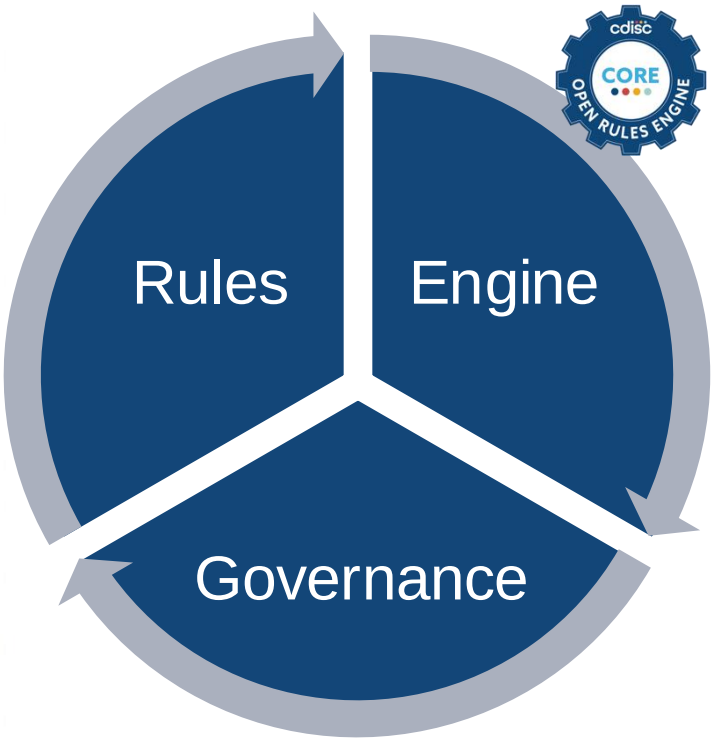
Organization: CDISC

Nick De Donder graduated as a biomedical scientist from the University of Ghent, Belgium in 2007 and has been employed since 2008 by Business & Decision Life Sciences at their headquarters in Brussels. He has been moving from being a Data Integration Specialist to Project Manager to Line Manager for the Data Standards team. Since 2020 he is Head of Data Standards. Nick is a member of the SDS team, an authorized CDISC trainer for CDASH, SDTM and Newcomers and a PHUSE committee member since 2017. In 2019 he joined the E3C and is now co-chairing it. Since June 2021 Nick has been program manager of the CDISC Open Rules project.

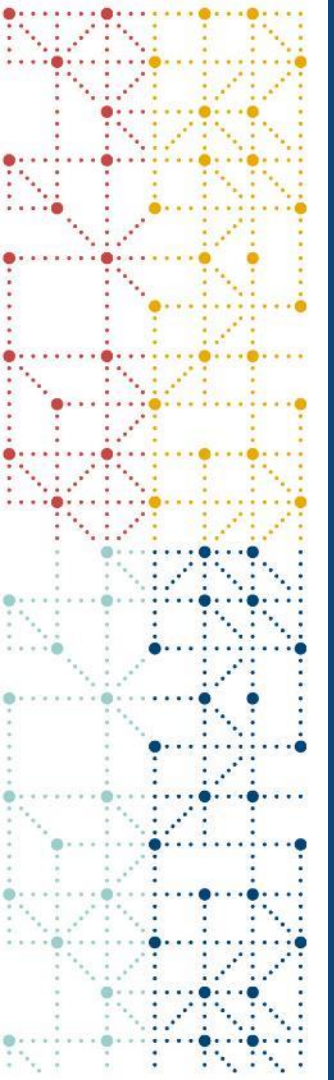
Agenda

1. Research Collaboration Agreement
2. FDA Business Rules
3. Into Practice
4. Progress
5. Next Steps

What are CDISC Open Rules?



- **Rules:** Complete set of aligned, open and unambiguous machine-readable conformance rules for each standard including CDISC, Regulatory, and Industry needs
- **Governance:** Well-defined governance model for the evaluation, development, and publication of rules from all stakeholders
- **Engine:** Open-source rules engine available for testing and community use



FDA Business Rules

Background

- Sponsors should evaluate their study data before submission against the conformance rules published by an SDO, the eCTD Technical Rejection Criteria for Study Data, and the FDA Business Rules.
- The Business Rules v1.5 (May 2019) help ensure that the study data are compliant, useful, and will support meaningful review and analysis. This applies to SDTM formatted clinical studies and SEND formatted non-clinical studies. For more information, see Section 8 of the Technical Conformance Guide.
- All business rules should be followed where applicable.

Research Collaboration Agreement with US FDA CDER & CBER

CDISC and FDA working together to develop machine-executable formats of the FDA Business Rules and on the development and ongoing governance of this set of executable rules within the CDISC Open Rules project that can be used by industry

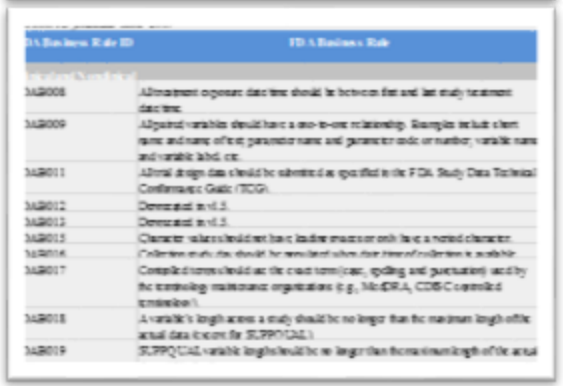
The benefits of creating a single source of truth for all FDA validation needs increases transparency for all stakeholders on how FDA checks data for conformance to CDISC standards and to existing FDA Business Rules

CDISC is Proud to Announce a Research Collaboration to Incorporate FDA Business Rules into CORE

Austin, TX – January 16, 2024 - CDISC is proud to announce a research collaboration with the U.S. Food and Drug Administration's Office of Translational Sciences in the Center for Drug Evaluation and Research and Office of Regulatory Operations in the Center for Biologics Evaluation and Research to incorporate FDA Business Rules into CDISC's Open Rules Engine (CORE).

CDISC's CORE project provides an open-source version of the CDISC Conformance Rules in a machine executable format. These rules, published and managed by CDISC, create a single source for conformance rules and allow industry vendors and sponsor companies to implement and extend these rules within their tools. FDA Business Rules are currently written in a plain text, non-machine executable format and describe the business requirements for regulatory review to help ensure that clinical trial study data is compliant and useful and supports meaningful review and analysis.

The goal of this effort, which began on November 3, 2023 and has term of three years, is to collaborate on providing input on machine-executable formats of the FDA Business Rules and on the development and ongoing governance of this set of executable rules within CORE



FDA Business Rule ID	FDA Business Rule
FDAB008	All treatment epoch start time should be between the first and last study treatment date/time.
FDAB009	All paired variables should have a one-to-one relationship. Examples include short name and name of test, parameter name and parameter code or number, variable name and variable label, etc.
FDAB011	All trial design data should be submitted as specified in the FDA Study Data Technical Conformance Guide (TCG).
FDAB012	Deprecated in v1.3.
FDAB013	Deprecated in v1.3.
FDAB015	Character values should not have leading spaces or only have a period character.
FDAB016	Collection study day should be populated when date/time of collection is available.
FDAB017	Controlled terms should use the exact term (case, spelling and punctuation) used by the terminology maintenance organization (e.g., MedDRA, CDISC controlled terminology).
FDAB018	A variable's length across a study should be no longer than the maximum length of the actual data known for SUPPQUAL.
FDAB019	SUPPQUAL variable length should be no longer than the maximum length of the actual

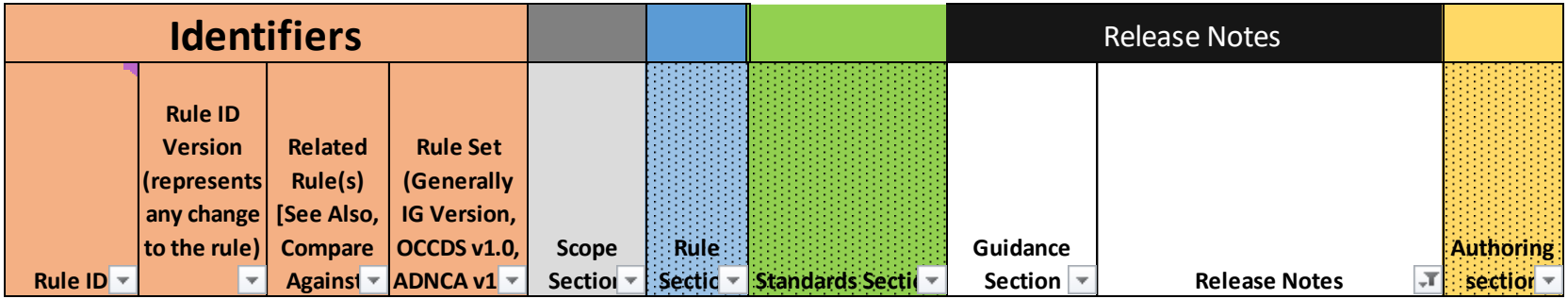
Into Practice

FDA Business Rules

Version 1.5 finalized June 2019	
FDA Business Rule ID	**FDA Business Rule**
Clinical and Nonclinical (SDTMIG, SEND)	
FDAB008	All treatment exposure date/time should be between first and last study treatment date/time.
FDAB009	All paired variables should have a one-to-one relationship. Examples include short name and name of test; parameter name and parameter code or number; variable name and variable label, etc.
FDAB011	All trial design data should be submitted as specified in the FDA Study Data Technical Conformance Guide (TCG).
FDAB015	Character values should not have leading spaces or only have a period character.
FDAB016	Collection study day should be populated when date/time of collection is available.
FDAB017	Controlled terms should use the exact term (case, spelling, and punctuation) used by the terminology maintenance organizations (e.g., MedDRA, CDISC controlled terminology).
FDAB018	A variable's length across a study should be no longer than the maximum length of the actual data (except for SUPPQUAL).
FDAB019	SUPPQUAL variable length should be no longer than the maximum length of the actual data within the dataset.
FDAB024	Large datasets should be split into smaller datasets no larger than 5 GB in size.
FDAB026	Records with a baseline flag should have a corresponding standard result with a standardized unit where available.
FDAB030	Standard units should be consistent within the same assessment (having the same --TESTCD, --CAT, --SCAT, --SPEC, --METHOD values).

Identifiers				Scope of Rule					
Rule ID	Rule ID Version (represents any change to the rule)	Related Rule(s) [See Also, Compare Against	Rule Set (Generally IG Version, OCCDS v1.0, ADNCA v1	Class	Subclass	Dataset or Domai	Variable	Elemen	Scope Sectio
FB0801	1			INT		EC, EX (merged w/DM)	--STDTC, --ENDTC, RFXSTDTC, RFXENDTC	ItemGroup Def ItemDef	
FB0901	1		All SDTMIG, SENDIG	ALL		ALL	Variable name and variable label		
FB0902	1		All SDTMIG, SENDIG	FND, TDM		All	--TESTCD, --TEST		
FB0903	1		All SDTMIG, SENDIG	SPC, TDM		DM, TA, TV, TE	DM.ARM-DM.ARMCD, DM.ACTARM-DM.ACTARMCD, TA.ARM-TA.ARMCD, TA.ACTARM-TA.ACTARMCD, TV.ARM-TV.ARMCD, TV.ACTARM-TV.ACTARMCD, TE.ELEMENT-TE.ETCD		
FB0904	1		All SDTMIG, SENDIG	TDM		TS	TS.TSVAL-TS.TSVALCD-TS.TSVALNF		
FB0905	1		All SDTMIG	INT		AG, CM, SU	--CLAS, --CLASCD		
FB0910	1		All SDTMIG	TDM		TI	TI.IETEST, TI.IETESTCD		

Harmonized spreadsheet



Identifiers							Release Notes		
Rule ID	Rule ID Version (represents any change to the rule)	Related Rule(s) [See Also, Compare Against	Rule Set (Generally IG Version, OCCDS v1.0, ADNCA v1	Scope Section	Rule Sectic	Standards Secti	Guidance Section	Release Notes	Authoring sectior

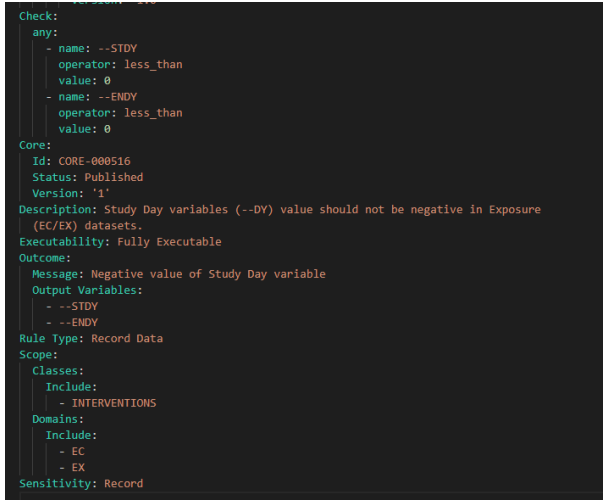
Business specification

Identifiers						Statement of Rule						
Rule ID	Rule ID Version (represents any change to the rule)	Related Rule(s) (See Also, Compare Against	Rule Set (Generally IG Version, OCCDS v1.0, ADNCA v1	Scope Sectio	Natural Language Rule (Success Criteria)	Rule (Success Criteria)	Condition (Success)	Natural Language Rule (Failure Criteria)	Rule (Failure Criteria)	Condition (Failure)	Error Message	Executabili
FB0801	1				All treatment exposure date/time should be between first and last study treatment date/time.	(RFXSTDTC <= --STDTC <= --ENDTC <= RFXENDTC	Variables exists and are populated; otherwise, account for all possibilities and treat with ANY conditions. Note: need functionality 'check for RFX--DTC availability in IG' for generic rule implementation. Note: NA for earlier SENDIGs that don't have RFX--DTC.	All treatment exposure date/time outside first and last study treatment date/time.	not (RFXSTDTC <= --STDTC <= --ENDTC <= RFXENDTC)	Variables exists and populated; otherwise, account for all possibilities and treat with ANY conditions.	All treatment exposure date/time outside first and last study treatment date/time.	Fully executable
FB0901	1		All SDTMIG, SENDIG			One-to-one		One-to-one mapping is not maintained.	Variable name and label pairing is not unique		One-to-one mapping is not maintained.	Fully executable
FB0902	1		All SDTMIG, SENDIG		TESTCD and TEST pair should have one-to-one relationship	One-to-one		One-to-one mapping is not maintained.	Pairing is not unique		One-to-one mapping is not maintained.	Fully executable
FB0903	1		All SDTMIG, SENDIG			One-to-one		One-to-one mapping is not maintained.	Pairing is not unique		One-to-one mapping is not maintained.	Fully executable
FB0904	1		All SDTMIG, SENDIG			One-to-one	TSVALCD ^= null	One-to-one mapping is not maintained.	Pairing is not unique		One-to-one mapping is not maintained.	Fully executable
FB0905	1		All SDTMIG			One-to-one		One-to-one mapping is not maintained.	Pairing is not unique		One-to-one mapping is not maintained.	Fully executable
FB0910	1		All SDTMIG			One-to-one		One-to-one mapping is not maintained.	Pairing is not unique		One-to-one mapping is not maintained.	Fully executable

Business rule to executability

FDAB036	The value for study day should not be negative for exposure treatments.

Identifiers					Statement of Rule							
Rule ID	Rule ID Version (represents any change to the rule)	Related Rule(s) [See Also, Compare Against	Rule Set (Generally IG Version, OCCDS v1.0, ADNCA v1	Scope Sectio	Natural Language Rule (Success Criteria)	Rule (Success Criteria)	Condition (Success)	Natural Language Rule (Failure Criteria)	Rule (Failure Criteria)	Condition (Failure)	Error Message	Executabili
FB3601	1				The value for study day should not be negative for exposure treatments.	--STDY > 0 and --ENDY > 0		The value for study day is negative for exposure treatments.	--STDY < 0 or --ENDY < 0			Fully executable



Test data

- Positive test data does not show issues

EPOCH	EXSTDTC	EXENDTC	EXSTDY	EXENDY
Epoch	*Start Date/Time of Treatment*	*End Date/Time of Treatment*	*Study Day of Start of Treatment*	*Study Day of End of Treatment*
Char	*Char*	*Char*	*Num*	*Num*
50	*50*	*50*	*8*	*8*
TREATMENT	2012-12-01	2012-12-01	2	2
TREATMENT	2012-12-02	2012-12-02	0	3
TREATMENT	2012-12-03	2012-12-03	4	4
TREATMENT	2012-11-30	2012-11-30	1	1

- Negative test data contains issues

EPOCH	EXSTDTC	EXENDTC	EXSTDY	EXENDY
Epoch	*Start Date/Time of Treatment*	*End Date/Time of Treatment*	*Study Day of Start of Treatment*	*Study Day of End of Treatment*
Char	*Char*	*Char*	*Num*	*Num*
50	*50*	*50*	*8*	*8*
TREATMENT	2012-12-01	2012-12-01	2	-2
TREATMENT	2012-12-02	2012-12-02	0	-3
TREATMENT	2012-12-03	2012-12-03	-4	-4
TREATMENT	2012-11-30	2012-11-30	-1	1

Results

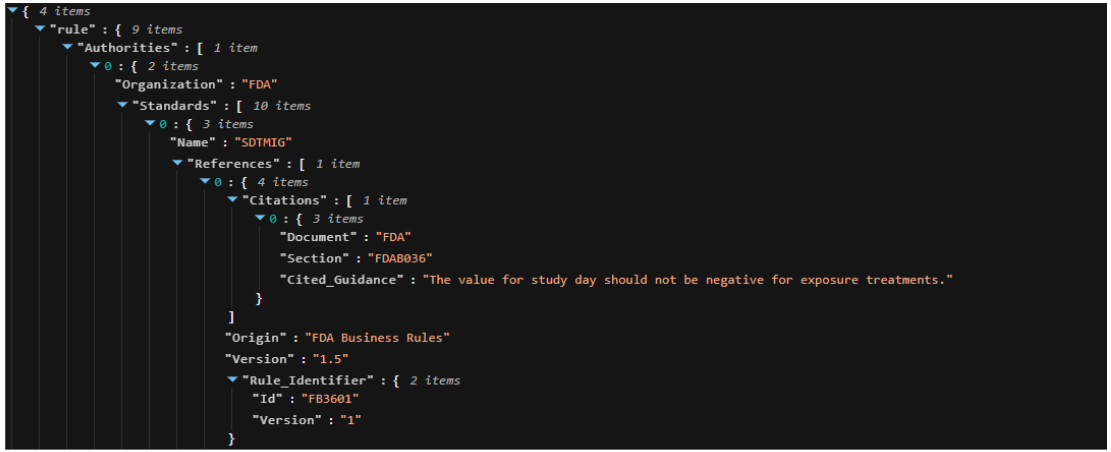
Results Positives 2

Request

Results

Results Negatives 7

Request



Results

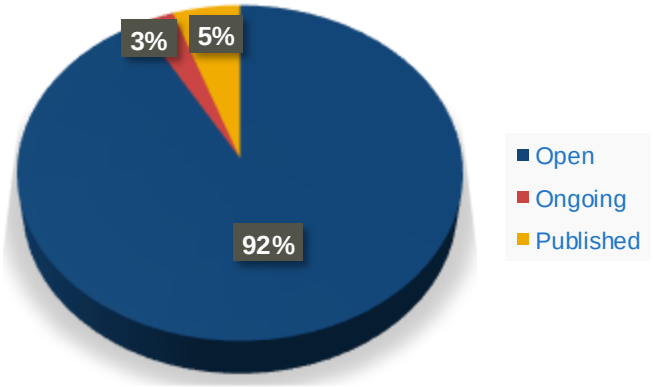
Executability

- Fully executable
- Partially executable
  - FDAB057: When collecting ethnicity demographic data from clinical trial participants, the following two minimum choices should be offered: "HISPANIC OR LATINO" or "NOT HISPANIC OR LATINO"
- Not executable
  - FDAB055: Trial participants should self-report race and ethnicity and they should not be assigned by the study team.
  - FDAB065: DS, CL, EG, EX, LB, MA, MI, PC, PP, and VS should be submitted if collected.

Progress

Status of the rules

- 48 new volunteers onboarded in February
- All rules specified by end of April



Next Steps

What's next

- Creating and testing all rules
- Providing unit test packages to FDA for reference
  - Positive and negative test data
  - YAML syntax and JSON code
  - Results
- FDA verification of published FDA Business Rules
- Specification of ADaM rules
- Testing by industry
- Adoption by the industry
- Ongoing maintenance following the governance process

Thank You!

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