Paper DS05

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

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ABSTRACT

In November 2023 FDA and CDISC started a three-year RCA (research collaboration agreement). The purpose of the RCA is the development and maintenance of FDA business rules as part of the CDISC Open Rules project. The CDISC Open Rules volunteers will create specifications that will become machine executable by writing the code in YAML and storing the rules in the CDISC Library. For the community it means a single version of the rules that is not interpretable and for FDA it means that all stakeholders will use the same rules, independent of the application used to run them.

In this presentation we want to show the process, development, and status of the rules. Furthermore, we will show how the community can contribute to this ongoing effort.

INTRODUCTION

The CDISC Open Rules Projects consists out of 3 parts: the rules, the governance of the rules and the engine.

The rules: a 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

Note that the name of the project has been changed to the CDISC Open Rules Project, however, the name CORE will still be used when we are talking specifically about the engine itself.

FDA BUSINESS RULES

BACKGROUND

According to the FDA Technical Conformance Guide (TCG) version 5.8 (September 2024) “Sponsors should evaluate their study data before submission against the conformance rules published by an SDO, the eCTD Technical Rejection Criteria for Study Data (See Appendix F), and the FDA Business Rules” (TCG section 8.2.2). On the FDA website (1) it says: “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.” Going back to the TCG (2) we can find that “All business rules should be followed where applicable”.

RESEARCH COLLABORATION AGREEMENT

In January 2024 CDISC and FDA signed a Research Collaboration Agreement (RCA) (3) which is valid for the next 3 years. As part of the RCA CDISC and FDA are 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.

INTO PRACTICE

In total there are 70 business rules that have been converted (specified) in the harmonized spreadsheet that has been used by the different foundational standards. 26 are both clinical and non-clinical, 17 are only for clinical and 27 are for non-clinical only. From these, 25 rules are not executable. All others have been converted in about 250 rules that can be written.

In the harmonized spreadsheet we indicate a number for the rule, in this case define them as FB (for FDA Business Rule), 2 numbers for making the link with the number of the business rule (FDAB056 becomes FB56) and 2 characters for the subset of the rule as some business rules can be converted into almost a 100 subrules to cover the intent of the rule. All rules are version 1.0 until a final version of the engine and the rules are published. There is a column for related rules as some FDA Business Rules are linked to already existing CDISC Conformance Rules. We do want to avoid having to write rules multiple time and also having multiple redundant outputs in the validation report.

In the file we also have different sections:

- The Scope section where we indicate the class, the domain, the variable the rule is applicable to.
- The Rule Section gives the natural language specification, the rule and he condition as both a success criterion and a failure criterion. It also indicated the executability of the rule.

- The Standards section is used to indicate for which version of a standard the rule is applicable to (SDTM or SEND and applicable version). In a final version of the rule this will be completed in the Rule Set of the Scope section, but we wanted to avoid having 12 rows for each rule.
- The Guidance section contains the information from the FDA Business Rules 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 Sectio	Rule Sectic	Standards Secti	Guidance Section	Release Notes	Authoring sectior

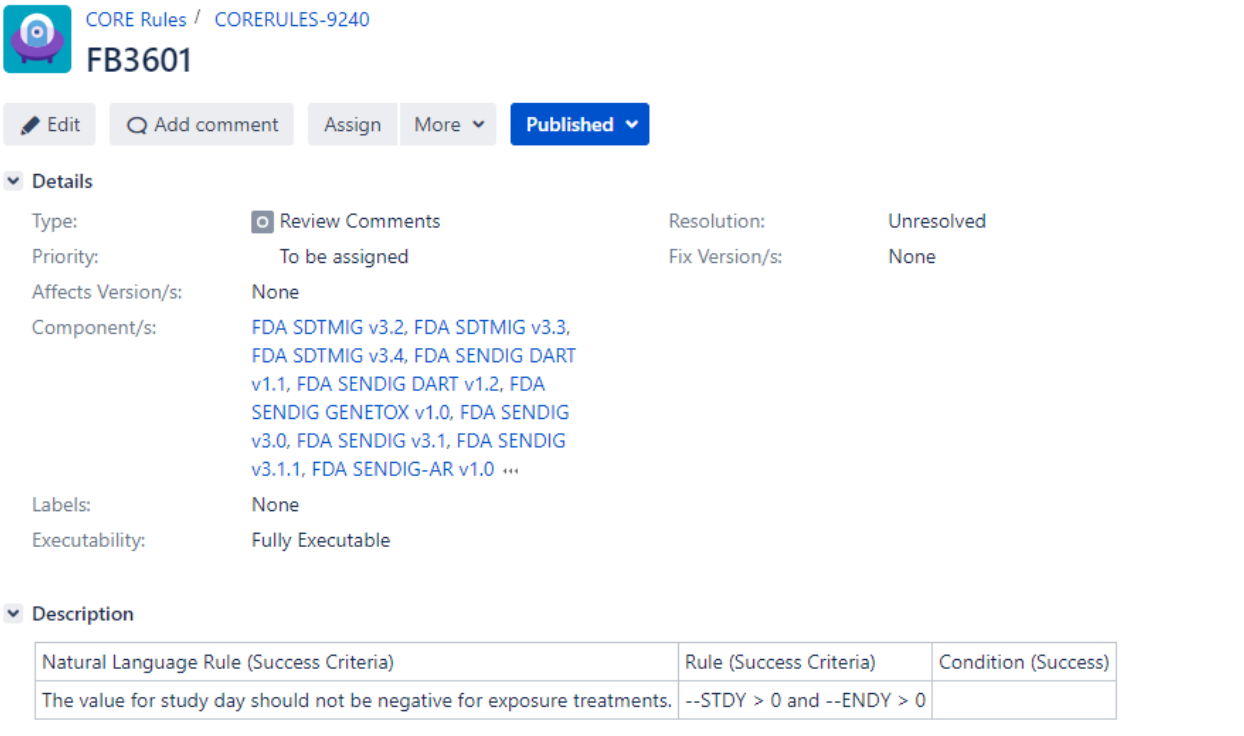
FROM BUSINESS RULE TO EXECUTABILITY

Let's see the process on how a rule is being converted from a specification to and executable version in YAML (Yet Another Markup Language). If we look at FDAB036 it says: "The value for study day should not be negative for exposure treatments".

We put this in the harmonized spreadsheet where the success criterion is the same as the business rule while the failure criterion is "The value for study day is negative for exposure treatments as we want the engine to provide an output when the data is not conformant. The rule has been translated as --STDY > 0 and --ENDY > 0. Of course --STDY and --ENDY can also not be 0 but that is not the scope of this rule.

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

When the rule has been specified, it goes through the JIRA process. The information gets added (name of the rule, applicable standards, executability and a description to make it easy) so a volunteer can take on the rule to start the writing process and the creation of test data. Afterwards another volunteer will perform the quality control to ensure the rule is doing what it is supposed to do, and whether the metadata is correct.



Rules are being written in the Rule Editor (4) in YAML code. The YAML code is very easy to read. In the Rule Editor, we write the rule as a failure criterion as we want it to provide an output if the condition is not met.

```yaml
Check:
  any:
    - name: --STDY
      operator: less_than
      value: 0
    - name: --ENDY
      operator: less_than
      value: 0
Core:
  Id: CORE-000516
  Status: Published
  Version: '1'
Description: Study Day variables (--DY) value should not be negative in Exposure
  (EC/EX) datasets.
Executability: Fully Executable
Outcome:
  Message: Negative value of Study Day variable
  Output Variables:
    - --STDY
    - --ENDY
Rule Type: Record Data
Scope:
  Classes:
    Include:
      - INTERVENTIONS
  Domains:
    Include:
      - EC
      - EX
Sensitivity: Record
```

Once the rule has been written we will perform unit testing by creating positive and negative test data. Positive data means that the data will not provide output when running on the data, negative test data will provide output.

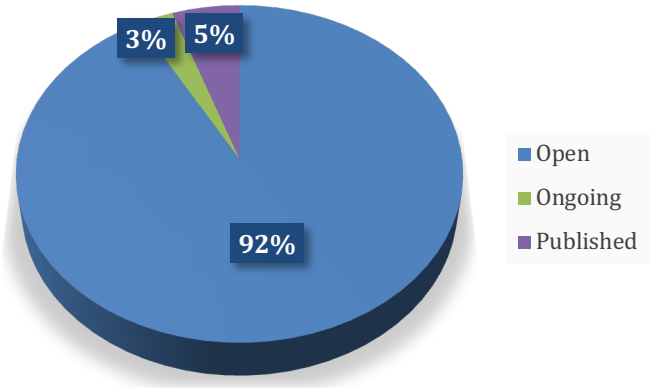
EXECUTABILITY

There are 3 statuses of executability: fully executable, partially executable and not executable.

- Fully executable is easy, we can write the rule, and it can provide an output.
- Partially executable means that a part of the rule can be executed. E.g. 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". The rule can check for the 2 values and whether they are correct, however, it cannot check the CRF whether these 2 options have been given.
- Not executable means that at this moment, the CORE engine cannot check whether the condition is true. E.g. FDAB055: Trial participants should self-report race and ethnicity and they should not be assigned by the study team. The engine cannot conform that someone else has entered the data.

STATUS OF THE RULES

After the press release CDISC organized a call for volunteers. 48 volunteers signed up in February and in March a training webinar was organized. By the end of April all the rules have been specified in the spreadsheet. At this moment only 9 rules have been published. Only 10% of the volunteers are still active so CDISC needs the active participation of volunteers and the community to make this project a success.



WHAT'S NEXT

The project will continue so the next steps is that all rules will be created and tested. Once the final set of rules has been created, the test unit packages will be provided to FDA reference. They will have the possibility to review the unit tests that have been performed. This will include the positive and negative test data, the rule in YAML syntax and JSON code and the results of the unit tests. FDA can use this for verification of completeness and correctness.
In the meanwhile, the team has started to map the business rules to ADaM specifications however a lot of the business rules will not be applicable for ADaM.
Once the rules are available we hope that the industry will start testing the rules and provide feedback to CDISC so improvements can also be made. The publication of the rules will hopefully also lead to the adoption by the industry. The ongoing governance will ensure that the rules remain up-to-date and accurate.

REFERENCES

(1) FDA Website: https://www.fda.gov/industry/fda-data-standards-advisory-board/study-data-standards-resources
(2) FDA Technical Conformance Guide: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/study-data-technical-conformance-guide-technical-specifications-document
(3) RCA press release: https://www.cdisc.org/news/cdisc-proud-announce-research-collaboration-incorporate-fda-business-rules-cdiscs-open-rules
(4) Rule Authoring tool: https://rule-editor.cdisc.org/

CONTACT INFORMATION

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