Complying with the ADaM Compliance Rules
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ABSTRACT

Is it hard to determine sometimes if we are living in a deluge of compliance rules for ADaM or a drought? There are multiple sources available: company specific, Pinnacle 21, PMDA, and CDISC; but what happens when they do not agree? What about when the compliance rules do not fully agree with the ADaM Implementation Guide? Or when there are not rules available for the latest Implementation Guide version? Lucky for us there is only one "official" version of the compliance rules available and are created by the CDISC ADaM team. While these rules are available, they have not always been easy to understand and implement – perhaps they even have some issues or false negatives. As a co-lead of the ADaM Compliance Rules sub-team, I have seen these challenges in depth and in detail. While this compliance document has been undergoing an overhaul for the next release of the ADaM compliance rules, this paper will be a user-friendly approach to using and understanding the compliance rules CDISC has released to date. Background to the ADaM Compliance sub-team's approach to building, defining, and creating these rules will be covered as well in order to highlight the potential differences the ADaM rules will have compared to SDTM and the other sources of rules which may be available to the industry.

INTRODUCTION

Study data standards make it possible for data consumers (including regulatory bodies) to receive consistently organized data across sponsors and therapeutic areas, streamlining the path to review and approval of life-saving medications. But how can sponsors and regulatory bodies evaluate whether the applicable data standard has been followed? The short answer is: compliance rules based in the applicable study data standard. After the ADaM Implementation Guide (ADaMIG) v1.0 was released, the ADaM team took charge of establishing the applicable compliance rules by establishing the ADaM Compliance sub-team. The ADaM Compliance sub-team released v1.0 of the compliance rules in 2010. Maintenance releases followed in 2011, 2012 and 2015.

Starting with the official ADaM compliance rules, sponsors and software vendors (including Pinnacle 21) developed applications to evaluate ADaM compliance. These applications are independent and take on the official ADaM team rules and often include additions to or variations on the ADaM rules based in sponsor or regulatory body (including PMDA) preferences. Over the last several years the ADaM compliance team has met and worked with members of both Pinnacle 21 and PMDA to help ensure that the official ADaM rules are accurate, fully supported in the ADaMIG, and appropriately applied. These joint investigations (supported by ADaM team review) have led to updates to the official ADaM rules, the ADaMIG and vendor applications.
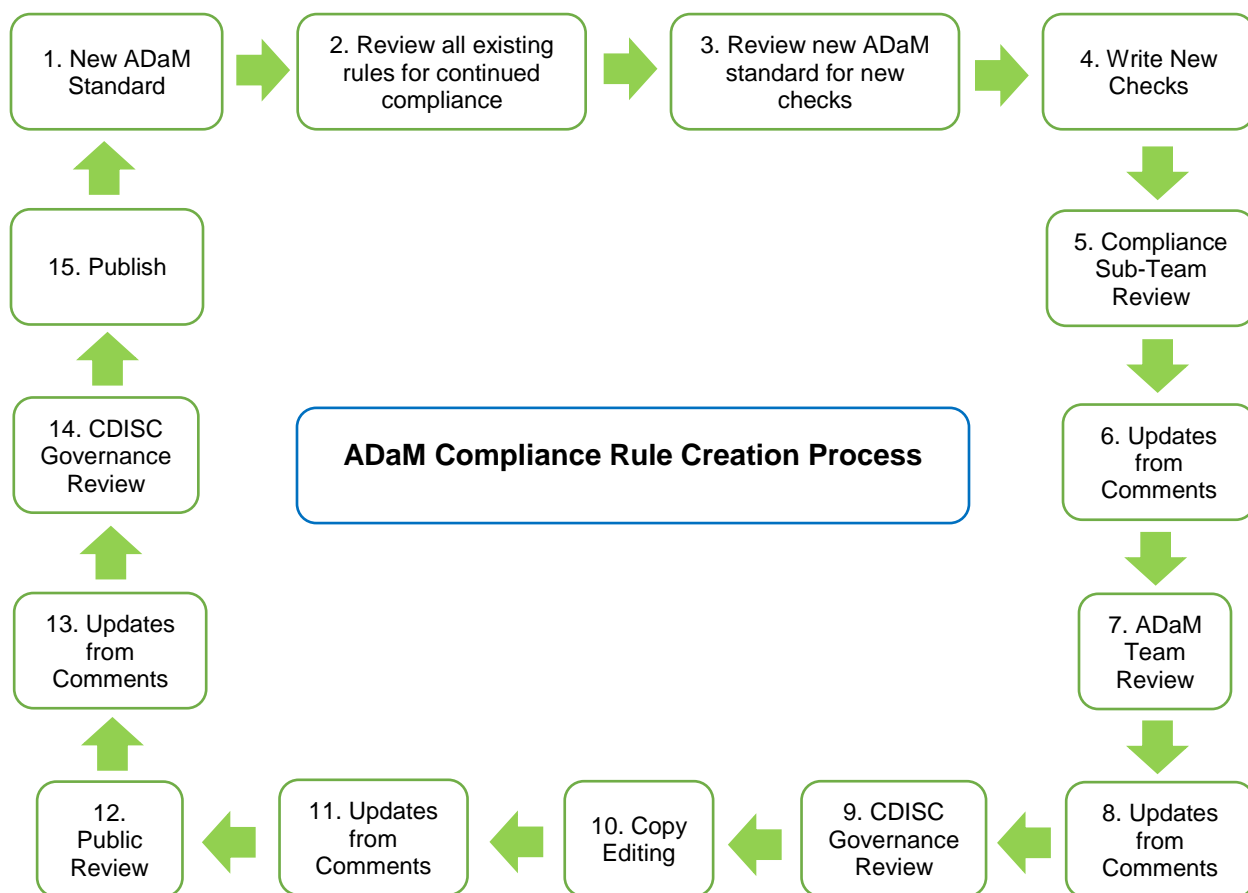
Standards implementation (including conformance review) is a process. Standards evolve and conformance rules based in the standards are generated, maintained and applied. In addition, sponsors need practical ways to ensure delivery of data that conforms to the applicable standard using the applicable compliances rules. Tough task, right? Keeping a few basic considerations in mind will remove much of the noise. What follows is an overview of the process used to generate and vet official compliance rules and some practical suggestions for how to avoid conformance issues. And just in case you are wondering, yes, there are pictures.

RULE CREATION BACKGROUND

Compliance Rule creation is not always a linear process and many steps require large amounts of time and discussion. Figure 1 shows a flow chart of the general process used to create compliance rules. The overall summary of this process is that a small subset of experts within the ADaM team create the compliance rules to be machine testable based on the ADaMIG. The product that is developed goes through several levels of review and subsequent updates before anyone outside of the CDISC ADaM volunteers sees the document. The public does have their chance to make comments near the end of the process, after which every comment is considered and a decision made as to whether or not to update the validation check. Finally, after all reviews and comments are done, the newest version of the validation rules is published. Having a wide variety of (often vocal) opinions is part and parcel of how good standards are established and maintained. Step 4 tends to be the most time consuming part of

this process because members of the ADaM Compliance Sub-Team need to agree that a rule is required and then to agree on wording of the rule.

Figure 1.

The newest version of the ADaM compliance checks will be released in a new format. A small example can be seen of this new draft format in Figure 2. Additional reference columns will be available to better accommodate multiple versions of a new standard document. In addition a new column for message type will be included which will categorize issues targeted by the compliance checks. Categories will include Error (Clear violation of the ADaMIG), Warning (issues that require additional documentation, an oversight in a published ADaMIG version which was fixed in a later version), and Note (data quality issues which may impact the integrity of an ADaM dataset). Please note: the ADaM Compliance Sub-Team only creates checks which are machine testable. ADaM has many concepts which are analysis driven and can't be checked without additional study knowledge; manual review is needed in addition to programmatic compliance review.
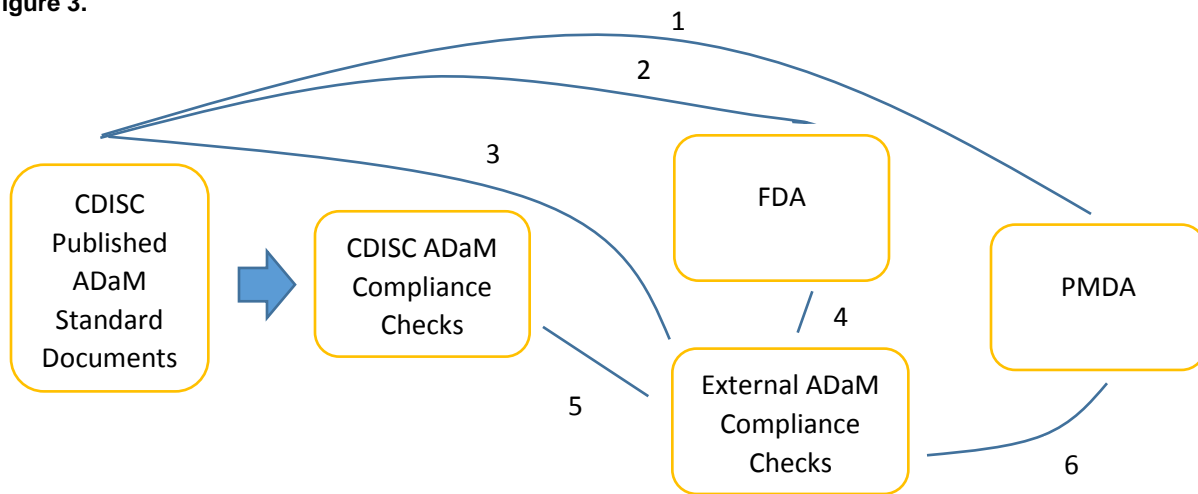
Figure 2.

Check Number	IG Version	ADaM Structure Group	Machine-Testable Failure Criteria	Message Type	Guide	Section	Item	Cited Guidance
1	1.0	ADSL	ADSL dataset does not exist	Error	Model v2.1 ADaM IG v1.0	6 2.3.1		CDISC-based submission of data from a clinical trial even if no other analysis datasets are submitted. IG: ADSL and its related metadata are required in a CDISC-based submission of data from a clinical trial even if no
1	1.1	ADSL	ADSL dataset does not exist	Error	Model v2.1 ADaM IG v1.1	6 2.3.1		CDISC-based submission of data from a clinical trial even if no other analysis datasets are submitted. IG: ADSL and its related metadata are required in a CDISC-based submission of data from a clinical trial even if no

ALL CHECKS ARE NOT CREATED EQUAL

It is important to remember that all compliance checks are not created equal. There is only one official source of ADaM compliance checks: which is the CDISC ADaM Compliance Sub-Team. External checks (anything not published through CDISC) can take a variety of routes as shown in Figure 3.   A good rule of thumb to follow is that any rule from an external source should never conflict with rules provided from CDISC without good reason and without appropriate documentation of the reasoning.

Figure 3.

WHEN THE CHECK DOES NOT EXIST

ADaM is an intentionally flexible model as datasets are modeled based on analysis needs. This is much different from SDTM which has a much stricter format and, in general, can be expected to look about the same with some small variations depending on what information is collected in the CRF. For SDTM, most potential conformance checks can be programmatically evaluated; for ADaM, a smaller percentage of compliance issues can be evaluated with code. Many requirements stated in the ADaMIG are based in specific study design details and cannot be evaluated in a vacuum. This is the primary reason why it is essential that ADaM spec writers, reviewers, and programmers have a thorough understanding of the ADaMIG before beginning their work. Is the study randomized? Is it a cross-over design? Which population flags are required in the SAP? These are just a few examples of analysis specific information which will affect manual ADaM compliance review.

In addition to not covering non-machine testable criteria, official CDISC compliance checks often are not available until after standards are approved for submission to the FDA and other regulatory bodies. Having a wide variety of (often vocal) opinions is part and parcel of how good standards are established and maintained but that discussion takes time. For example, the Occurrence Data Structure (OCCDS) v1.0 is commonly used but official CDISC checks have not yet been published. Though these checks will be out for public review from CDISC soon, there is nothing in the meantime.

When official compliance rules are needed but not yet available, standards experts need to manually review the datasets for compliance to the published IG. And with no official support from CDISC, review applications typically default to the most closely applicable rules available. For example, OCCDS format datasets will generate an Error in a Pinnacle21 report because PARAM and PARAMCD are missing as the application assumes OCCDS data are following the BDS structure. The source of such issues (for example, the data structure "Is acceptable per OCCDS v1.0") will need to be documented for submission. Informed manual review for ADaM compliance is unavoidable; and in addition to addressing issues that cannot be tested with code, manual review can inform programmatic review findings.

TIPS FOR AVOIDING NON-COMPLIANCE

The easiest way to avoid non-compliance in an ADaM dataset is to plan in advance. Too often non-compliance is found after a study is all but complete which makes it difficult and time consuming to fix the issues. There are a variety of places in the course of a study where planning will keep non-compliance to a minimum. First, start at the very beginning – using CDASH CRFs and compliant SDTMs will make creating compliant ADaM datasets much more straight forward. Then, make sure to review frequently. Review the ADaM specs for compliance before programming gets underway. Review the ADaM datasets for compliance before TFL programming begins. Review the ADaM datasets after any updates from TFL findings as well. Do not let the study get off track due to review cycles – plan at the beginning of a study for various review cycles, count it into the timelines!

In order to eliminate most compliance issues is to have the programmers of the ADaMs be knowledgeable of ADaM standards. Basic ADaM training is important for any programmer who will be working on programming ADaM datasets. While the protocol and SAP are on the required reading list for anyone working on the study, the ADaMIG as well as any Therapeutic Area User Guide (TAUG) standards which are applicable should also be on this list to read for any person working on CDISC compliant ADaM datasets.

CONCLUSION

The CDISC compliance check creation process can be time consuming, and the most recent release is not considering the newest ADaM standards. There are a variety of ways to use these structures in a compliant format in the meantime. Make sure the checks being used adhere to the ADaMIG of choice and ensure all proper documentation is in place for any checks which are not followed. When compliance checks do not exist, then make sure an expert in CDISC standards reviews the ADaM dataset for adherence to the version of the ADaMIG in use. Plan in advance for checking compliance, and complying with the ADaM Compliance Rules will be much easier!

The ADaM Compliance Sub-team is working steadily toward a new release of ADaM validation checks which will include edits to ADaMIG v1.0, ADAE and new checks for ADaMIG v1.1 and OCCDS v1.0. Remember – public review of the next version of the CDISC ADaM Validation Checks document will be soon, let your voice be heard by participating in the review!

RECOMMENDED READING

- ADaM Implementation Guide v1.0 & v1.1

- Occurrence Data Structure v1.0

- Therapeutic Area User Guides

- ADaM Validation Checks v1.3

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