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ADaM is back: The new ADaM IG 1.2 and beyond

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ABSTRACT

In 2018 several previews of the new ADaM Ig were made [1], at both CDISC Interchanges all around the world and at PhUSE conferences, but it was only last October the final version was released. At first glance, the new Ig does not seem to contain a lot of new concepts and idea. However, with a more critical and in-depth review, we can clearly see what was the effort of the entire team to release the new Ig. Despite the Ig comes with a very detailed revision history, with this presentation I would like to provide an in-depth review of what has changed. This is not just limited to present new variables, but it is also about reviewing the most critical changes in "wordings" e.g. to clarify specific ADaM implementation aspects. I will also take the opportunity to provide an update on current CDISC ADaM development.

INTRODUCTION: ADAM STANDARDS WHERE DO WE STAND

Available Versions

It was in 2009 when the first Implementation Guidance (IG) was released together with ADaM standard model version 2.1 and this is still the current version of the standard in use. In that version of the standard, the fundamental principles of the ADaM standards were 'declared' together with the AdaM classes ADSL and BDS, while the third class, the occurrence data structure or OCCDS, will be released few years later and described in a separate document. In 2016 the ADaM IG version 1.1 was released, and this is still based on the data model version 2.1.

There were then some additional items and idea not finalized in 2016 and implemented in IG 1.1 that have been finally implemented with the IG 1.2 released last year.

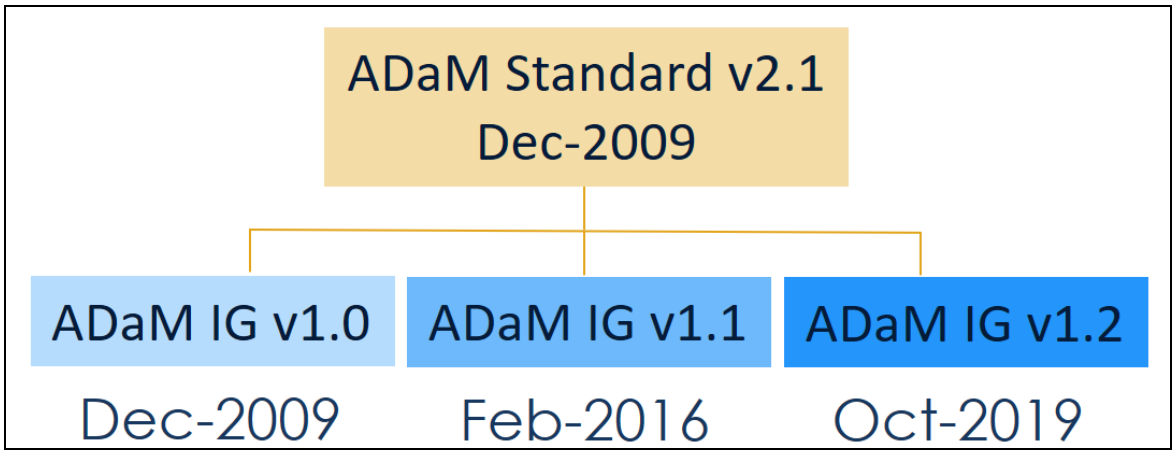

Figure 1: ADaM Available Versions

Other CDISC documents relevant to the ADaM standards have been released throughout the years by the CDISC ADaM Team. In particular:

- the ADaM structure for Occurrence Data where the third ADaM class was officially released in 2016 and this was based on the pilot ADAE
- the define.xml supplement for analysis results metadata, a set of additional metadata needed to describe key statistical outputs

- two documents containing some additional implementation examples, the ADaM Examples in Commonly Used Statistical Analysis Methods and the ADaM Basic Data Structure for Time-to-Event Analyses
- we should not forget that ADaM has its own standard controlled terminology of which the last version was released last June

Function	Publication Date
ADaM Examples in Commonly Used Statistical Analysis Methods v1.0	Dec-2011
The ADaM Basic Data Structure for Time-to-Event Analyses v1.0	May-2012
ADaM Structure for Occurrence Data (OCCDS) v1.0	Feb-2016
ADaM Data Structure for Adverse Event Analysis v1.0*	May-2012
Analysis Results Metadata Specification v1.0 for Define-XML Version 2	Jan-2015
ADaM Controlled Terminology**	2020-06-26

*Superseded by OCCDS v1.0 **Current Version

Table 1: Other ADaM Documents to Consider

Conformance Rules

Like for other CDISC standards, also ADaM has its own set of conformance rules to verify the compliance of the ADaM datasets developed using the ADaM model. Although officially no conformance rules have been released yet to support IG 1.2, the rules defined in the conformance rules version 2.0 are mostly applicable to version 1.2 too.

The two set of conformance rules supporting IG 1.0 and 1.1 are implemented in the latest version of the software developed by Pinnacle21.

Regulatory Agency Requirements

Regarding versions supported by the regulatory agencies, the latest IG 1.2 is not yet supported by both FDA and PMDA, with the PMDA still requiring version 1.0

When submitting clinical data to health authorities in standard formats, the individual agencies might have additional requirements in their technical conformance guidance, and this is also true for ADaM. For example, the requirement to have at least one analysis dataset in the submission named ADSL or to have in the submission at least one dataset referenced in the data definition file as containing the primary efficacy variables. These are additional recommendations FDA has made with its Study technical conformance guidance

Other Resources for ADaM Implementation

The CDISC TAUGs do also contains ADaM implementation examples for specific TA or indication.

As you can see from figure 2, starting from 2013, more and more the TAUGs started to incorporate some ADaM examples and recommendations, while before SDTM and controlled terminology were the main topics covered by the guidance.

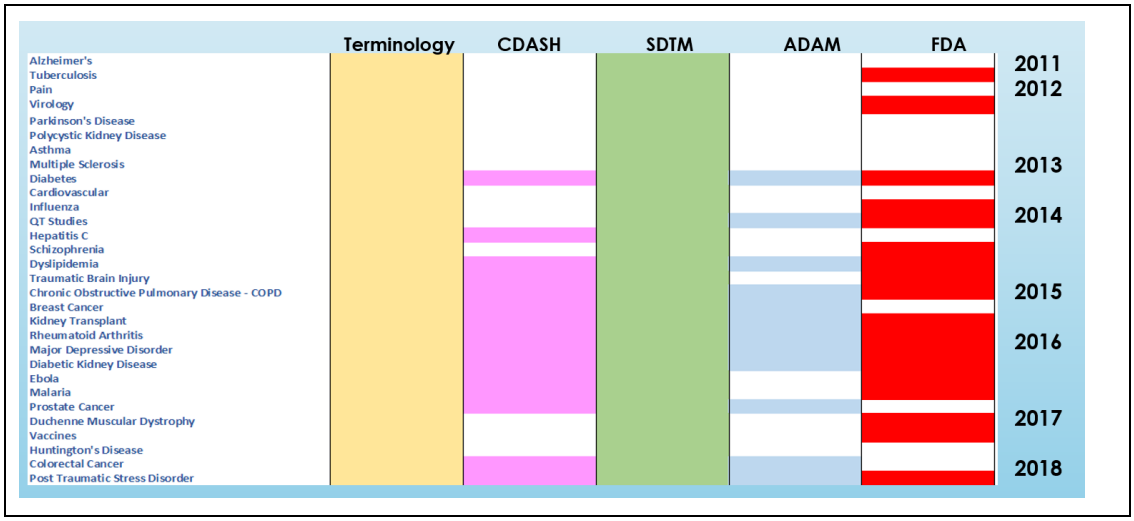

Figure 2: CDISC Therapeutic Area User Guidance (TAUG)

The following are just some examples extrapolated from the existing TAUGs [2]:

- Breast TAUG
    - Use of Intermediate ADaM datasets in deriving complex efficacy endpoints i.e. Progression Free Survival
    - Identification of Cancer Related 'Baseline Characteristics' i.e. Staging
- Diabetic Kidney Disease
    - Good Example of Composite Endpoints
    - Make use in ADaM dataset of AP-- prefix for variables belonging to Associated Persons so that they are not confused with subject variables
- Rheumatoid Arthritis
    - Use of pre-ADSL
- Diabetes – ADaM Supplement
    - Examples of Analysis Results Metadata
    - Randomization Stratification Factors in ADSL

Some of the recommendations coming from the individual TAUGs and became official recommendations and later implemented in the IG; for example, the concept of pre-ADSL proposed by the Rheumatoid Arthritis team have been incorporated in the IG 1.2. Same for the Randomization Stratification factors variables in ADSL, these were recommended in the Diabetes ADaM Supplement

ADaM IG 1.2 WHAT'S NEW

OVERVIEW

At first glance, the new IG does not seem to contain a lot of new concepts and idea. However, with a more critical and in-depth review, we can clearly see what was the effort of the CDISC ADaM Team to release the new IG.

We should not forget that creating a new standard, or release a new version of an existing standard, it is not an easy "task"; you need first to make sure you do not introduce anything that could contradict other existing standards that might be related to ADaM. Moreover, you need to make sure that any change in a sentence or a new entire section, does not cause misunderstanding in the reader (user).

Overall, the new IG does not introduce fundamental changes to the three ADaM classes, although some new standard variables added in both ADSL and BDS. The OCCDS, the Occurrence Dataset Structure class, it is still not incorporated in the IG document but part of the standard and described in a separate document as mentioned earlier.

Furthermore, the release of the new IG was the opportunity to clarify some sections that caused some misunderstanding in previous versions through the addition of additional description or improvement of some wording.

NEW VARIABLES IN ADSL

A set of new standard variables were added in ADSL to contain randomization strata values, both "as randomized2 and "as verified" that is when the clinical data related to the stratification factors are finally verified and confirmed.

<u>Randomization Strata Variables</u>

The new variables allow for maximum flexibility in representing:

- the description of the randomization factors
- the values used for randomization
- the values that were verified

Up to nine different stratification factors can be defined (see figure 3)

Random / Verified	Strata Concatenation	Description of Stratification Factor	Stratification Factor Value
As Randomized	STRATAR(N)	STRATwD	STRATwR(N)
Verified (actual)	STRATAV(N)		STRATwV(N)

Figure 3: New Randomization Strata Variables

For example, let's consider an oncology study where a balanced block randomization schema stratified by age category and stage of disease was used (figure 4). A subject was randomized in the strata age 18-55 and stage of disease I/II; when the stage of disease was finally confirmed by the histology assessment after the randomization, the stage was finally defined as stage III and this information is derived in ADaM using a different set of randomization strata variables ending with a 'V' for verified. Instead, the verified Age strata was confirmed to be the same as the one communicated at the time of the randomization.

As Randomized

SUBJID	STRATAR	STRAT1D	STRAT1R	STRAT2D	STRAT2R
1	18-55, I/II	Age	18-55	Stage of Disease	I/II

Verified (actual)

SUBJID	STRATAV	STRAT1D	STRAT1V	STRAT2D	STRAT2V
1	18-55, III	Age	18-55	Stage of Disease	III

Figure 4: Example of Use of New Randomization Strata Variables

NEW VARIABLES IN BDS

The BDS class contains essentially two groups of new variables:

- a set of variables to store information about change to baseline, as opposite to the change from baseline
- a set of variables to support the analysis of bi-directional toxicity analysis

I will focus on the second group of variables that were proposed by the ADaM oncology sub-team and finally integrated and generalized in the IG 1.2.

New Variables in BDS - Bi-Directional Lab Toxicity Variables

The ADaM IG 1.1 was containing already some variables to derive the toxicity grade. A classic example is the set of toxicity criteria defined by the US-NCI, the NCI-CTCAE criteria[1] where, for certain lab parameters, a classification of the severity ranging from grade 1 to grade 4 is defined based on the observed lab values, with '0' used as a convention for summary tables when the lab values are not abnormal.

However, there are some criteria that are bi-directional such as the ones defined for Sodium as shown in figure 5, where you can have toxicity criteria based on low values (hypo-toxicity) but also on high values (hyper-toxicity).

Toxicity / CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4
↑ Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L	>160 mmol/L
↓ Hyponatremia	<LLN-130 mmol/L	125 - 129 mmol/L	120 - 124 mmol/L	<120 mmol/L

Figure 5: Example of NCI-CTCAE bi-directionality

As mentioned before, with ADaM Ig 1.1 only one toxicity variable was available, ATOXGR, and BTOXGR for baseline toxicity. Thus, we can use this variable to derive the toxicity grade as per the example in figure 6. However, there were no variables to distinguish between hypo-toxicity and hyper-toxicity neither a common approach was suggested in the IG.

[1] "Common Terminology Criteria for Adverse Events (CTCAE)", Version 5, https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

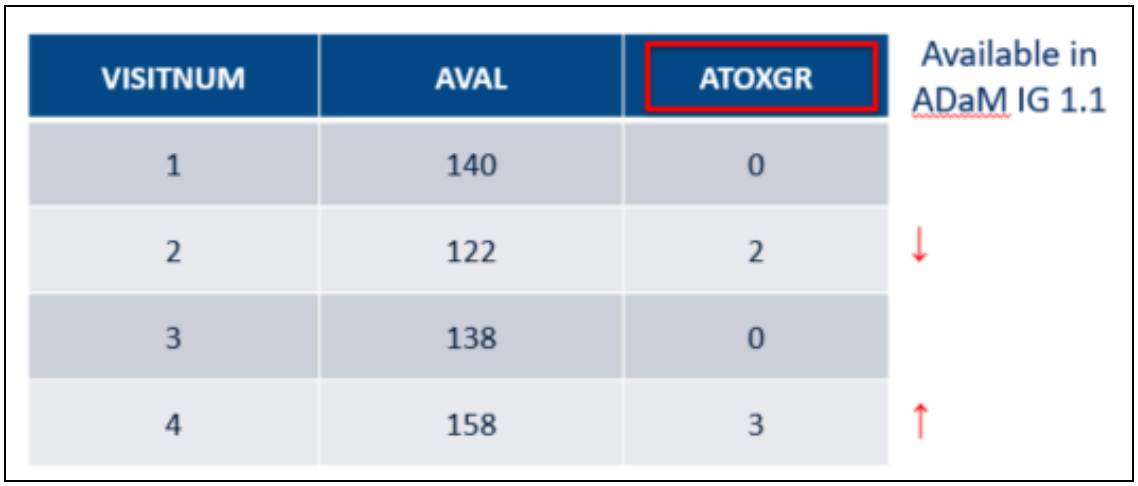

Figure 6: A subject sodium experience PARAMCD=NA / PARAM=Sodium (mmol/L) with ADaM IG 1.1

Different approaches were considered by the CDISC ADaM team, including the option of adding new records, one considering the high toxicity criteria and another one considering the low toxicity criteria.

The final decision was to add a pair of new variables in IG 1.2 to handle the lab toxicity when low, those ending with 'L', and another pair to handle lab toxicity when high, those ending with H. With these new variables you can not only store the toxicity grade but also the definition of the toxicity according to the classification criteria; in the example in figure 7 the NCI-CTCAE defines low values as Hyponatremia and high values as Hypernatremia. From the example in figure 7, obviously, for the same lab value you can have a toxicity in one direction or in the other or in none direction, and in that case for both toxicity definition the toxicity grade is set to '0'.

With this approach, you have an ADaM dataset that is analysis-ready, meaning that you can easily build an output table for all type of toxicity criteria by simply selecting the hyper- toxicity or hypo-toxicity type and their associated severity grade.

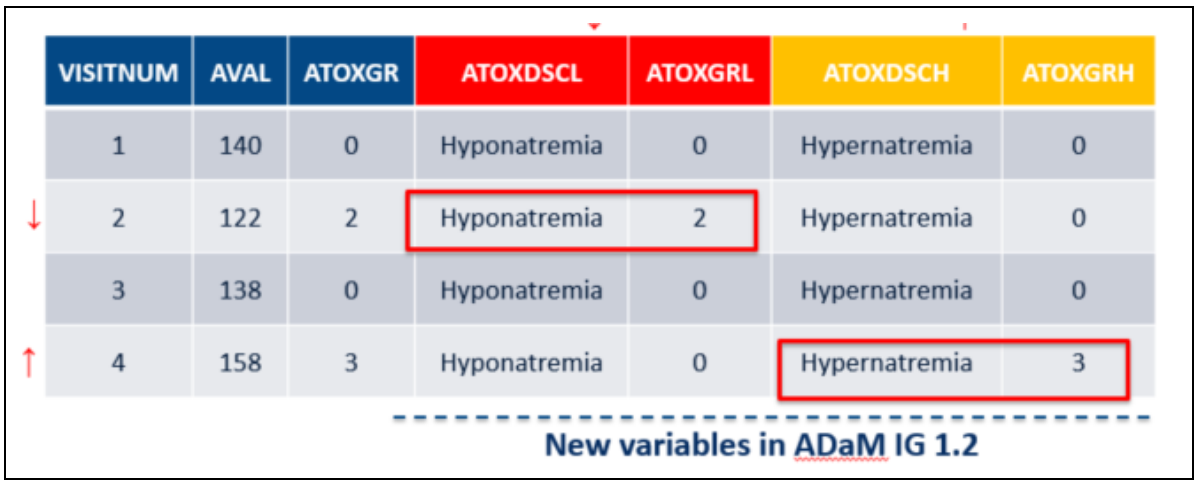

Figure 7: A subject sodium experience PARAMCD=NA / PARAM=Sodium (mmol/L) with ADaM IG 1.2

Figure 8 details the entire set of variables and their purpose.

The example in figure 9 instead is for Platelets where the toxicity criteria are defined in one direction only, Platelet Count Decreased, making not applicable the 'High' variables, which will be in this case not applicable and therefore Null.

If you are not considering yet to use ADaM IG 1.2, I would like to emphasize the fact new variables added in IG 1.2 do not deviate any of the ADaM standard rules, so in my opinion both set of variables added in ADSL and BDS can be used even if you are using ADaM IG 1.1.

Variable Name	Variable Label	Comment
ATOXGRL	Analysis Toxicity Grade Low	To assess when a subject's lab value falls within the low toxicity range
BTOXGRL(N)	Baseline Analysis Toxicity Grade Low	To establish the shift in toxicity level from baseline level when a subject shifts to lower grade
ATOXDSCL	Analysis Toxicity Description Low	To describe the low end of the lab test criteria preferred term
ATOXGRH	Analysis Toxicity Grade High	To assess when a subject's lab value falls within the high toxicity range
BTOXGRH(N)	Baseline Analysis Toxicity Grade High	To establish the shift in toxicity level from baseline level when a subject shifts to higher grade
ATOXDSCH	Analysis Toxicity Description High	To describe the high end of the lab test criteria preferred term

Figure 8: BDS - Bi-Directional Lab Toxicity Variables

VISITNUM	AVAL	ATOXGR	ATOXDSCL	ATOXGRL	ATOXDSCH	ATOXGRH
1	180	0	Platelet count decreased	0		
2	88	1	Platelet count decreased	1		
3	32	3	Platelet count decreased	3		
4	10	4	Platelet count decreased	4		

Figure 9: BDS - Bi-Directional Lab Toxicity Variables with toxicity criteria in one direction only

OTHER CHANGES

Other changes have been introduced in IG 1.2:

- In the ADaMIG that went for public review, the Parameter Qualifier PARQUAL was added as a new variable. However, the ADaM leadership team has determined that further development of the concept was needed and therefore not approved the new variable, making probably most of you unhappy
- PARAMTYP was the source of confusions regarding difference with DTYPE, so the variable was finally deprecated since also its purpose can be covered by describing the derivation of the new parameters in the metadata; however, it can be still used if required by individual sponsors if operationally 'needed'
- The concept of pre-ADSL is also introduced in situations where highly derived variables are to be included in ADSL, where yet the derivation of these variables may be better performed in another ADaM dataset. With this approach better traceability can be achieved (see figure 10)

The new IG has also other changes, such as BASETYPE variables populated for applicable parameters only, a clarification of the relationship between primary and secondary variables, ADSL timing variables vs Other ADaMs and some recommendations on how to handle traceability when the Multiple Imputation method is used. For more details I recommend reading the PHUSE paper [1].

Example of added clarification / wording change

Among the wording changes, one in particular clarifying the purpose of ADSL was made in section 2.3.1 of the IG:

In a study there is only one dataset in the class "SUBJECT LEVEL ANALYSIS DATASET",
and its name is ADSL Any other datasets with one record per subject would be members of other classes

This statement also clarify the fact that not all subject level characteristics need to be mapped or created in ADSL and other ADaM datasets can be created to store other Subject-level variables i.e. specific study disease variables. So the message here is that you do not need to "squeeze" all subject level variables into ADSL and other Subject Level Datasets can be created to contain other baseline characteristics.

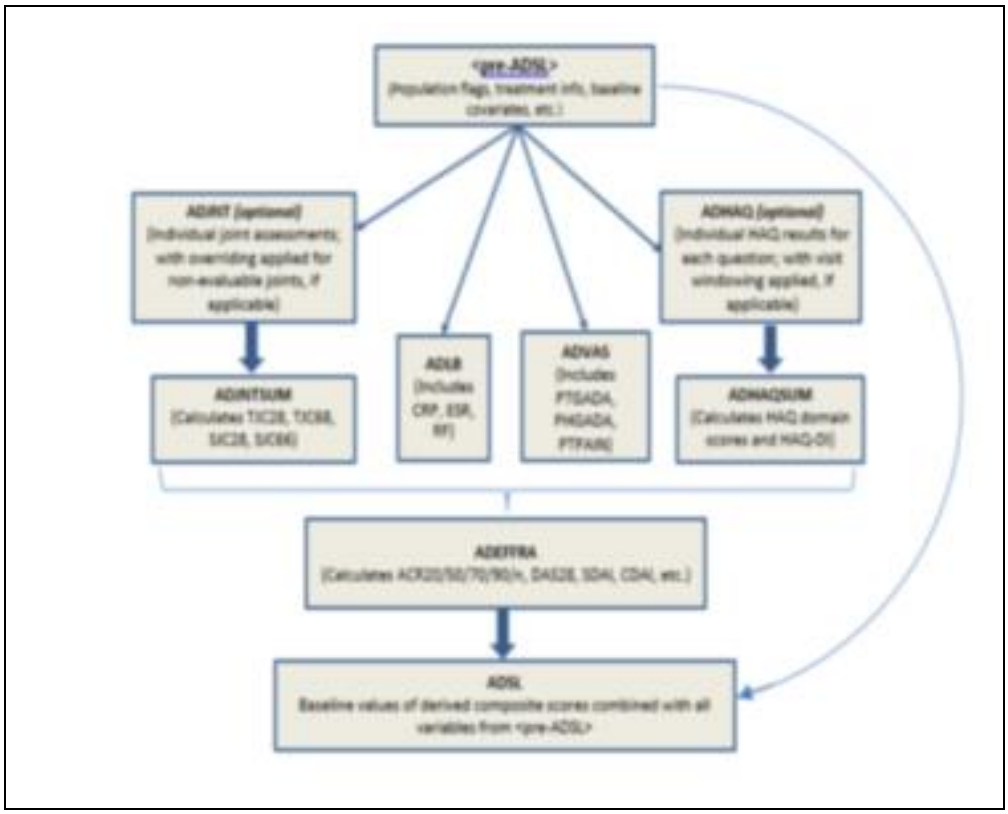

Figure 10: The concept of pre-ADSL

ADaM FOR THE FUTURE

The ADaM team has a taught delivery schedule for 2020-2021. There are in fact a number of planned deliverables for which release or update on timeline can be checked at https://www.cdisc.org/standards/in-development:

- ADaM Conformance Rules v3.0: a set of conformance rules are planned to be released for this year. These set of updated rules will include specific checks for supporting IG 1.2 enhancements
- ADaM Medical Devices: a document to describe how to apply the current ADaM standard structures in medical-device-studies
- ADQR Supplements: GDS-SF Suppl: an ADaM supplements to the SDTM QRS documents as a guidance for creating CDISC-compliant ADaM datasets for the analysis of Questionnaires
- ADaM OCCDS v1.1: a New version of ADaM OCCDS which will include more complex examples, but no major changes to the class are expected
- ADaM Traceability Examples: an ADaM Traceability document (see later)
- ADaM PK Analysis: an ADaM PK Analysis document with specific BDS examples to support the analysis of non-compartmental analysis (NCA)
- ADaM Oncology: an ADaM Oncology guidance document to include structures, variables, and examples specific for the analysis of oncology studies.

ADAM TRACEABILITY EXAMPLES

The "ADaM Traceabiliy Examples" document is one of the most interesting, and probably useful document; its release is planned in 2021. The development of the document is well advanced and a preview made last year at PharmaSUG in the US [3].

This document will be another source of good end-to-end examples, focusing on on how to guarantee clear traceability in ADaM through either data or metadata traceability.

These are just some of the implementation examples covered in the document:

- Use of Intermediate Dataset(s)
- Traceability with Parameters from multiple Input Datasets
- Traceability when using look-up table
- Multiple imputations

The examples cover a wide variety of practical scenarios where traceability can be at risk if proper design of ADaM

datasets and their metadata not implemented.

ADAM FOR INTEGRATION

The probably most awaited guidance, the "ADaM Data Structures for Integration", its release is unfortunately somehow on hold as it requires careful review and assessment by the different governance CDISC bodies and probably the acceptance of the regulatory agencies.

Although I would not suggest using such approach systematically, the approach presented by Zhong et al. [4] can be considered in individual ISS / ISE[1] submission if previously confirmed with the individual agency reviewers.

CONCLUSIONS

Despite no major changes, in IG 1.2 there are some important and useful improvements. Moreover, implementation examples are increasing common and there will be more coming; the intent here is to reduce different interpretations of the guidance and the models. However, there are still other documents to consider when using and implementing the ADaM standards.

Overall, there are still some gaps in the ADaM standards, but I would say in the CDISC standards in general, when integrating data from several studies is required in support of either ISS or ISE.

REFERENCES

1. "Incremental Changes: ADaM IG v1.2 Update" - T. Peterson and B Harris; PHUSE 2018
2. "A Systematic Review of CDISC TAUGs" - A. Tinazzi, PharmaSUG-China; 2019
3. "More Traceability: Clarity in ADaM Metadata and Beyond" – W. Zhong, R. Watson, D. Ewing and J. Zhang; PharmaSUG 2019
4. "ADaM Structures for Integration: A Preview" – W. Zhong, K. Minkalis, D. Bauer; PharmaSUG 2018

RECOMMENDED READING

The Good Data Submission Doctor - New ADaM Implementation Guidance – Cytel Blog
https://www.cytel.com/blog/new-adam-implementation-guidance

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

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[1] ISE=Integrated Summary of Efficacy / ISS=Integrated Summary of Safety