PharmaSUG 2024 - Paper DS-204

ADaM Discussion Topics: PARQUAL, ADPL, Nadir

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ABSTRACT

This paper and presentation will cover three topics that have been under varying levels of discussion within the CDISC ADaM team but are not part of the standard. First is the parameter-qualifier variable PARQUAL, which can be found in a couple Therapeutic Area User Guides (TAUGs), went out for public review as part of ADaMIG v1.2, but currently breaks BDS rules because it never made it into a final publication. Second is ADPL, a one-record-per-subject-per-participation dataset that might be useful for studies where subjects can enroll more than once or have multiple screening attempts, similar to the proposed SDTM DC domain. Third is Nadir variables, like Change from Nadir and Percent Change from Nadir, not currently allowed in a BDS structure. In each case, the paper and presentation will summarize CDISC ADaM team discussions and give personal (not CDISC-authorized) recommendations of when and how to implement these concepts in order to meet analysis needs.

INTRODUCTION

I've been part of the CDISC ADaM team since 2001. Things have changed over the years, but what hasn't changed is that content can be under discussion for years before it ever gets out to the public. Additionally, content that comes out in a document for public review can be changed dramatically or removed entirely from the final product. For example, some of you may recall that a variable PARQUAL came out in the draft ADaMIG v1.2 for public review, but it wasn't part of that final version.

It takes time to get an industry standard developed through CDISC. Team members represent many companies, including pharma, biotech, vendors, and regulatory agencies. Before going out for any public review, the following steps are followed:

1. A standardization need is identified.
2. The team, in this case the ADaM team, pulls together a sub-team with a team leader or co-leaders, tasked with developing a draft document to address that need.
3. Once that draft is completed, it is brought to the full ADaM team for review and comment.
4. The sub-team reviews and addresses all comments, creating an updated document.
5. That draft is brought to the broad CDISC team for review and comment.
6. The sub-team reviews and addresses all comments, creating an updated document.
7. That version is set out for public review and comment.

Once the public review period is complete, the following steps are followed:

1. The sub-team reviews and addresses all comments and creates an updated document.
2. Contentious comments may go to the ADaM full team or the higher-level CDISC team for input.
3. A final version must be accepted by the ADaM full team and the broader CDISC team before final publication.

All these check-ins along the way ensure that the final document will be acceptable by industry and useable by regulatory agencies. However, development, review, modifications, and check-ins all take time, especially when the bulk of the ADaM team is comprised of volunteers who do this work in addition to their "day" jobs. We want standards that are applicable to our industry and developed by people who

will be using them, but how do you squeeze in the time when you're involved in a submission deliverable that your company is depending on?

As you can imagine, it is not unusual for a topic to be initiated at a meeting and a proposal agreed on, but it is then pushed out to be part of a future document that is years in the making.

Because there are quite a few of these topics piling up in the preparation for the next ADaM document, I wanted to give a sneak preview of a few of them and make some recommendations on what you can do in the interim. These topics seem to have some agreement within the team; however, none are in any official CDISC ADaM document, and I can't guarantee that they ever will be.

PARQUAL

All versions of the ADaMIG (v.1.0, 1.1, 1.2, 1.3) state "PARAM must include all descriptive and qualifying information relevant to the analysis purpose of the parameter". This allows analysis and review to make use of a single variable, PARAM (Parameter Name), to describe the result. That means when bringing over a test from SDTM to use in analysis, you often need to tack on content from some SDTM qualifiers to construct a parameter. Table 1 shows a few ADaM parameters and the variables from SDTM needed to create them.

PARAM content	SDTM variables needed
Weight (kg)	VSTEST, VSSTRESU
Supine Systolic Blood Pressure (mmHg)	VSPOS, VSTEST, VSSTRESU
Urine Glucose (mg/dL)	LBCAT, LBTEST, LBSTRESU

Table 1: ADaM Parameters Constructed from Multiple SDTM Variables

Over the years the ADaM team has discussed some cases where it might be helpful to have some qualifier information outside of PARAM. This would make analysis simpler when the qualifier is described in a table title or section header, rather than with the rest of the parameter. The team went as far as to create a qualifier variable named PARQUAL that was intended to be part of ADaMIG v1.2. At that time, some of the Therapeutic Area User Guides (TAUGs) were being developed, and PARQUAL was included in a couple of them. The FDA also uses PARQUAL in at least one of their documents. Figure 1 shows how PARQUAL is used in the Prostate Cancer TAUG to describe the assessor ("INVESTIGATOR REVIEW" or "INDEPENDENT REVIEW"):

adtte.xpt

Row	STUDYID	USUBJID	TRTP	PARAM	PARQUAL	PARAMCD	AVAL	CNSR
1	ABC-123	ABC-123-001	A	Progression-free survival (months)	INDEPENDENT REVIEW	PFS	10.8090349075975	0
2	ABC-123	ABC-123-001	A	Progression-free survival (months)	INVESTIGATOR REVIEW	PFS	15.8090349075975	0
3	ABC-123	ABC-123-002	A	Progression-free survival (months)	INDEPENDENT REVIEW	PFS	3.81108829568789	0
4	ABC-123	ABC-123-002	A	Progression-free survival (months)	INVESTIGATOR REVIEW	PFS	3.81108829568789	1
5	ABC-123	ABC-123-003	A	Progression-free survival (months)	INDEPENDENT REVIEW	PFS	25.7905544147844	1
6	ABC-123	ABC-123-003	A	Radiographic Progression-free survival (months)	INVESTIGATOR REVIEW	PFS	25.7905544147844	1
7	ABC-123	ABC-123-004	A	Progression-free survival (months)	INDEPENDENT REVIEW	PFS	7.68788501026694	1

Figure 1: Part of the Prostate Cancer TAUG ADTTE example

There was great concern among many ADaM team members about the potential for misuse or abuse of PARQUAL, and the team was unable to come up with a solution that would allow PARQUAL to be used in some situations but not in others. Due to this issue, between the draft ADaMIG v1.2 and the final version, PARQUAL was completely removed and has not yet found a home in any ADaM document.

PARQUAL has continued to be brought up in team discussions, and different proposals have been made to "put a fence" around PARQUAL so that it would be used for only the qualifiers the ADaM team feels are appropriate. The use of non-extensible controlled terminology (CT) seemed like a good solution, and could work for something like assessor as used in the Prostate TAUG. However, the other case for

PARQUAL where the ADaM team sees a need is with drug name, such as used in PK or exposure analysis, and it is impossible for CT to keep with the all the drug names under development.

More recently, the ADaM team is looking at a solution that adds another variable, possibly called PARQTYPE (Parameter Qualifier Type) that is subject to non-extensible controlled terminology and must be used whenever PARQUAL is used. Table 2 shows how the pair of variables would be used:

PARQUAL	**PARQTYPE (tentative name)**
Parameter Qualifier	Parameter Qualifier Type
Contains the qualifying text needed to fully describe PARAM	Is one of the allowed types of qualifications
Not subject to CDISC CT	Uses CDISC Non-Extensible CT
Must be used with variable PARQTYPE	Must be one of the CDISC CTs

Table 2: Proposed Use of PARQUAL and PARQTYPE

This solution would allow PARQUAL to be used only in certain specific conditions. Conformance rules developed for both PARQUAL and PARQTYPE would allow you to discern whether PARQUAL is used correctly:

- A check can fire if PARQUAL is used without PARQTYPE
- A check can fire if PARQTYPE is not one of the terms in the CDISC CT

Additionally, there is already a process in place for proposing new terms to existing CT, so the ADaM team can use that process to evaluate each proposal in a timely manner.

While it may not be perfect, this solution seems reasonable and I expect will happen. If finalized, existing documents using PARQUAL, such as the Prostate TAUG, would need updating to add PARQTYPE.

Until/unless a solution for PARQUAL is finalized, you might consider doing one of the following:

1. Do not use PARQUAL. Put all qualifying information into PARAM or create separate datasets for each “qualifier” (e.g., one dataset for investigator review and one for independent review).
    - Advantage: breaks no rules
    - Disadvantage: might make programming some outputs a little more difficult
2. Use PARQUAL only in situations that the ADaM team is currently planning to allow (Assessor, Drug Name) and be clear in the ADRG how PARQUAL was used.
    - Advantage: Matches existing TAUG use cases which are likely to be part of a future standard
    - Risks: Compliance tool messages will need to be explained, plus it is possible that PARQUAL won’t be part of any upcoming standard
3. Use PARQUAL for any single qualifier that you want to pull out of PARAM.
    - Risks: Compliance tool messages will need to be explained, plus it is less likely that anything other than Assessor and Drug Name will be part of the use cases for PARQUAL
4. Use PARQUALy for any number of qualifiers that you want to pull out of PARAM.
    - Risks: Compliance tool messages will need to be explained, plus it is highly unlikely that more than one component will be allowed to be pulled out of PARAM

Note that I didn’t mention PARQTYPE in any of the choices above. I feel that it’s probably not worth including this variable until defined by ADaM. That also means that checking for compliance would need to be a manual step.

My recommendation is to do choice 1 if that doesn’t feel too constraining, and even choice 2 doesn’t seem very risky. I strongly advise against choices 3 and 4, since these are exactly the reasons the ADaM team is looking to restrict PARQUAL.

ADPL

Sometimes a subject can participate in a study more than once, such as screen failure subjects who retry, or enrolling with different parts of the body.

ADSL is structured as one record per unique subject (USUBJID). Structuring it as one record per subject per participation (SUBJID) will fire conformance rules, not work with some tools that are expecting ADSL to be one record per USUBJID, and may cause issues with regulatory reviews. For these reasons, it is probably not a good idea to include multiple participations in ADSL as new rows.

In 2022, the CDISC SDTM team proposed the use of domain DC, structured as one record per SUBJID, for studies where subjects could have multiple participations. DC would be used in addition to DM, and it would be a sponsor decision to determine which DC record would be used in DM. Along with DC, the SDTM proposal allowed SUBJID to be added to any other domains, meaning merging by SUBJID can be done between DC and those datasets, similar to how ADSL is merged by USUBJID to other datasets.

The ADaM team began discussions on adding an analysis participation-level dataset that is similar to ADSL but with a row for each participation (SUBJID). Since SUBJID is already allowed on any ADaM dataset, this participation-level dataset would be straightforward to combine with other ADaM datasets.

A participation-level ADaM dataset was described in a paper and presentation at the 2023 PharmaSUG conference, titled “ADaM Datasets with Multiple Participations per Subject”. It notes that a participation-level ADaM dataset can currently be used without breaking any ADaM rules by following these recommendations:

1. Continue to produce ADSL as one record per USUBJID.
2. Create additional dataset ADPL as one record per SUBJID, when needed, and use it to append core variables to other ADaM datasets that break down analysis by participation. Since there is no “one record per participation” ADaM structure, use class ADAM OTHER for submission.
3. Explain in the ADRG when and how to use ADSL vs. ADPL.

Below is an example of a subject who enrolled in a study more than once, where their vital signs analysis needs to be performed based on each participation. Here,

- Table 3 shows a few pertinent ADPL variables, and
- Table 4 shows some pertinent ADVS variables, where ADPL content has been used to derive ADY and TRTP.

USUBJID	SUBJID	TR01SDT	TRT01P
ABC-01	ABC-01	02MAY2023	A
ABC-01	ABC-25	15OCT2023	B

Table 3: Example ADaM ADPL for one subject

USUBJID	SUBJID	PARAM	AVAL	ADT	TR01SDT	ADY	TRTP
ABC-01	ABC-01	Height (cm)	167	01MAY2023	02MAY2023	-1	A
ABC-01	ABC-01	Weight (kg)	68	01MAY2023	02MAY2023	-1	A
ABC-01	ABC-01	Weight (kg)	65	22MAY2023	02MAY2023	21	A
ABC-01	ABC-25	Height (cm)	167	16OCT2023	15OCT2023	-1	B
ABC-01	ABC-25	Weight (kg)	66	16OCT2023	15OCT2023	-1	B
ABC-01	ABC-25	Weight (kg)	67	30OCT2023	15OCT2023	16	B

Table 4: Example ADaM ADVS for one subject, using ADPL for reference values

The ADaM team is in discussions about adding an ADPL dataset and potentially an ADPL class. Until that happens, you can create a ADPL dataset but use class ADAM OTHER. This solution doesn't break any ADaM rules.

NADIR

Nadir is the lowest value within a parameter. Analysis of Nadir, Change from Nadir, and Percent Change from Nadir are common in Pharmacokinitics reporting and can also be used with other types of data.

The ADaMIG has a BDS rule for adding columns that states, "A parameter-invariant function of AVAL and BASE on the same row that does not involve a transform of BASE should be added as a new column". But Nadir is not a function of AVAL and BASE, since it requires that you look across all rows within the parameter to find the lowest value. Change from Nadir and Percent Change from Nadir would require AVAL and the Nadir variable, so these are also not compliant as variables in a BDS dataset.

Some members of the ADaM team treat Nadir as a baseline to get around this issue. For example,

- Table 5 show four rows of one subject and parameter with a typical change from baseline. Nadir is not addressed here at all.
- Table 6 creates a new dataset with the same AVALs, but where instead Nadir is flagged as baseline and used to derive the change from baseline values. This second dataset essentially has the same number of rows and columns, but the values of variables BASE, CHG, and ABLFL are different. A unique dataset name, dataset label, and explanation in the define.xml will be needed to clarify the purpose of each dataset (ADXYZ and ADNADIR).
- Table 7 is basically a combination of Table 5 and Table 6. Think of it as adding a second baseline that is the Nadir value into the original dataset in Table 5. Since now there are two records used as baseline within the same subject and parameter, this dataset must include variable BASETYPE. BASETYPE doesn't have CT, but here I've used "LAST NONMISSING" to describe the regular baseline and "NADIR" to describe Nadir. Note that this solution essentially doubles the number of rows in the original dataset (Table 5) and will need some explanation in the ADRG on how to subset down to the appropriate rows for each analysis (such as by using BASETYPE).

row	**PARAMCD**	**AVAL**	**BASE**	**CHG**	**ABLFL**
1	ABC	10	10	0	Y
2	ABC	15	10	5	
3	ABC	5	10	-5	
4	ABC	20	10	10	

Table 5: Dataset ADXYZ Change from Baseline for one Subject and Parameter

row	**PARAMCD**	**AVAL**	**BASE**	**CHG**	**ABLFL**
5	ABC	10	5	5	
6	ABC	15	5	10	
7	ABC	5	5	0	Y
8	ABC	20	5	15	

Table 6: New Dataset ADNADIR where Nadir is used as Baseline

row	PARAMCD	AVAL	BASE	CHG	ABLFL	BASETYPE
1	ABC	10	10	0	Y	LAST NONMISSING
2	ABC	15	10	5		LAST NONMISSING
3	ABC	5	10	-5		LAST NONMISSING
4	ABC	20	10	10		LAST NONMISSING
5	ABC	10	5	5		NADIR
6	ABC	15	5	10		NADIR
7	ABC	5	5	0	Y	NADIR
8	ABC	20	5	15		NADIR

Table 7: ADXYZ Adding Nadir as a 2nd Baseline Using BASETYPE

Treating Nadir as a baseline might meet the BDS rules, but it feels clunky and potentially inappropriate. Fred Wood, former CDISC SDS team lead, would speak of "hijacking" variables for a purpose other than what was intended, and, in my opinion, this is what is being done when you treat Nadir as a Baseline.

But what other options are there, when your analysis need calls for content like Nadir, Change from Nadir, etc. as variables? Well, one way is to create this content as columns, as shown in Table 8:

row	PARAMCD	AVAL	BASE	CHG	ABLFL	NADIR	NADCHG	NADFL
1	ABC	10	10	0	Y	5	5	
2	ABC	15	10	5		5	10	
3	ABC	5	10	-5		5	0	Y
4	ABC	20	10	10		5	15	

This breaks the BDS rule, but there's no reason you couldn't use dataset class ADAM OTHER rather than calling it BDS.

The ADaM team is discussing adding Nadir variables to BDS in the next version. Until that happens, you can do the following to enable Nadir analysis:

1. Add Nadir variables to the BDS dataset, giving it a class ADAM OTHER. This is 100% compliant, but it might make it difficult to do much compliance checking on the parts of the dataset that are supposed to be BDS-compliant.
2. Add Nadir variables to the BDS dataset, and still call it BDS. This breaks the current BDS row vs. column rule, but it could be explained in the ADRG since this is done specifically to enable analysis.
3. Use BASE, CHG, PCHG for Nadir content, either in the same dataset with variable BASETYPE or in a separate dataset. I personally don't recommend this because it feels like those variables are being hijacked for a purpose other than what was intended.

CONCLUSION

This paper covered 3 situations that are under discussion within the CDISC ADaM team and I believe are likely to be part of a future ADaM document. If you have study needs where these would apply, consider how to handle each situation:

PARQUAL: In situations where you have the same parameter for different assessors or for different drug names, consider whether to use variable PARQUAL to hold the assessor or drug name such that the combination of PARAM and PARQUAL is needed to determine uniqueness. Although this breaks a BDS rule, it follows some of the CDISC TAUGs and can be justified in the ADRG.

ADPL: For studies where a subject can participate more than once, create a participation-level analysis dataset (ADPL), similar to ADSL but structured as one record per SUBJID. Use the ADAM OTHER class for dataset ADPL. Use the combination of ADSL and ADPL for your different analysis needs, ensuring that every dataset which needs to analyzed by participation includes variable SUBJID. In the ADRG, describe how ADSL and ADPL are used. This breaks no current ADaM rules.

NADIR: For variables such as Nadir which are needed on the same row as AVAL for analysis, consider adding them as variables. To be ADaM compliant, this dataset would need to be called ADAM OTHER. If you choose to call it BDS because everything else about the dataset conforms to BDS rules, then describe this non-compliance in the ADRG.

Watch for future publications and draft review opportunities from the CDISC ADaM team. Consider joining the team if you want to be involved in making decisions like these.

REFERENCES

CDISC ADaM documents available at https://www.cdisc.org/standards/foundational/adam.

CDISC SDTM documents available at https://www.cdisc.org/standards/foundational/sdtm.

CDISC SDTMIG documents available at https://www.cdisc.org/standards/foundational/sdtmig.

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