PharmaSUG 2024 - Paper DS-193

# Around the Data DOSE-y Doe, How Much Fun Can Your Data Can Be: Using DOSExx Variables within ADaM Data Sets

Inka Leprince, PharmaStat, LLC;
Richann Jean Watson, DataRich Consulting

## ABSTRACT

In the intricate dance of clinical trials that involve multiple treatment groups and varying dose levels, subjects pirouette through planned treatments - each step assigned with precision. Yet, in the realms of pediatric, oncology, and diabetic trials, the challenge arises when planned doses twirl in the delicate arms of weight-adjustments. How can data analysts choreograph the Analysis Data Model (ADaM) data sets to capture these nuanced doses?

There is a yearning to continue with the normal dance routine of analyzing subjects based on their protocol-specified treatments, yet at times it is necessary to learn a new dance step, so as not to overlook the weight-adjusted doses the subjects actually received. The treatment variables TRTxxP/N in the Subject-Level Analysis Dataset (ADSL) and their partners TRTP/N in Basic Data Structure (BDS) and Occurrence Data Structure (OCCDS) are elegantly designed to ensure each treatment glides into its designated column in the summary tables. But we also need to preserve the weight-adjusted dose level on a subject- and record-level basis. DOSExxP and DOSExxA, gracefully twirl in the ADSL arena, while their counterparts, the dashing DOSEP and DOSEA, lead the waltz in the BDS and OCCDS data sets. Together, these harmonious variables pirouette across the ADaM data sets, capturing the very essence of the weight-adjusted doses in a dance that seamlessly unfolds.

## INTRODUCTION

While some dancing is a precise art, there are some dance styles which allow some leniency. The Clinical Data Interchange Standards Consortium (CDISC) DOSE variables are of the latter style, allowing data analysts to choreograph their data to fit their analysis needs. This paper uses a fictitious pediatric clinical trial as a case study and provides implementation issues, standard solutions, and examples of these dosing variables, crafting a symphony of precision in the clinical dance.

This dosing dance demands not just finesse but also the preservation of weight-adjusted dose level on a subject- and record-level basis.

## CDISC STANDARDS

In the dynamic landscape of clinical research and healthcare, the standardization of data collection, management, and reporting is paramount for ensuring efficiency, interoperability, and data quality. CDISC develops and promotes data standards that support the acquisition, exchange, submission, and archive of clinical research data and metadata. These data standards are required for submissions by regulatory authorities such as the United States' Food and Drug Administration and Japan's Pharmaceuticals and Medical Devices Agency (CDISC Website, 2024).

CDISC standards provide a common framework for organizing and structuring data sets and associated metadata across the lifecycle of clinical trials. At the core of CDISC's standards are models, standards, and controlled terminology designed for traceability, efficiency, replication, and review of clinical trial data (CDISC ADaM Team, 2009). Of relevance, key CDISC standards include the ADaM, which provides a data framework for the traceability and analysis of clinical trial data.

There are four fundamental principles of the ADaM that are deliberate and precise. These four principles enable a smooth and traceable elegant flow in data analysis. (Watson, 2022)

1. Traceability fosters transparency and accountability. Traceability acts as the guiding rhythm, facilitating a clear and unambiguous path from analysis results back to their source data, akin to dancers effortlessly tracing their movements back to the music.

2. Analysis-ready data are poised to generate insights swiftly. Just as a dancer must be poised and ready to perform, data must be analysis-ready, analysis data sets should be designed to be one procedure away from producing analysis results.
3. Metadata plays a crucial role in understanding the context of analysis. Metadata serves as the detailed choreography notes, providing descriptions of data sets, variables, and parameters, ensuring everyone is on the same page.
4. Readily usable software. The requirement of usable software ensures that the dance floor is open to all, as analysis data sets are compatible with commonly available software tools, promoting inclusivity and collaboration in the dance of data analysis.

According to ADaM Implementation Guide (ADaMIG) v1.3 and ADaM Structure for Occurrence Data Implementation Guide (ADaM OCCDS) v1.1, there are three basic data set structures:

1. **Subject-Level Analysis Dataset (ADSL**): As with each dance routine, there is a foundational step. Within the ADaM performance, the ADSL is our foundational step. ADSL is designed to capture and present analysis-ready data in a format suitable for statistical analysis. The ADSL is structured as a flat table, where each row represents a unique subject and each column represents a specific variable or attribute. The data set is designed to be comprehensive, capturing all relevant subject-level data necessary for analysis across different domains of interest. Subject-level information typically includes but is not limited to: demographic information (e.g., age, sex, race), baseline characteristics, treatment assignments, subject disposition, and population flags (CDISC ADaM Team, 2021).
2. **Basic Data Structure (BDS):** The BDS data structure supports the majority of parametric and nonparametric analyses. Within this structure, there can be multiple records per subject, per analysis parameter, per analysis timepoint, much like different dance moves performed by the same dancer throughout the routine (CDISC ADaM Team, 2021). A BDS data set is typically recognized by having the variables PARAM and AVAL, which capture the analysis parameter and analysis value, respectively.
3. **Occurrence Data Structure (OCCDS)**: The OCCDS extends the capabilities of ADaM by addressing the need to analyze data related to occurrences or events of interest within a clinical trial. It provides a standardized framework for capturing and analyzing data associated with specific occurrences, such as adverse events, or concomitant medications. (CDISC ADaM Team, 2016). An OCCDS data set is typically recognized by having a –TERM or –TRT variable, which stores the verbatim term of the event or the reported name of drug (CDISC ADaM Team, 2016).

Analysis data sets that follow the ADaM fundamental principles and other ADaM conventions, but which do not fit in the 3 defined structures (ADSL, BDS, OCCDS), are considered to be ADaM data sets with a class of OTHER (CDISC ADaM Team, 2009).

## CASE STUDY: SPIN

Using a fictitious pediatric clinical trial as a case study, Study of Pediatric Ingestion of Norteño* (SPIN): A Randomized Trial. This hypothetical single-center, randomized, Phase 2 study will evaluate the efficacy and safety of up to 28 days of treatment with Norteño in pediatric subjects with “two left feet”. The dose assignment for the pediatric population of this study is based on three adult-equivalent doses of study drug Norteño: 5 mg once daily (QD), 10 mg QD, and 20 mg QD. In reality, the doses dispensed and taken by the pediatric subjects are weight-adjusted to their individual body sizes. The pediatric subjects receive an adult-equivalent dose, which includes a range of doses from 1 mg QD through 20 mg QD as shown in Table 1.

* Norteño is a fictitious drug. It is only used for illustration of the concepts. It is not meant to represent any investigational product.

**Table 1 Conversion to Adult-equivalent Dose Based on Weight Class**

| | Adult-equivalent Dose of Norteño | | |
|---|---|---|---|
| **Weight Class** | **5 mg QD** | **10 mg QD** | **20 mg QD** |
| 20 –< 35 kg | 1 mg | 2.5 mg | 5 mg |
| 35 –< 50 kg | 2.5 mg | 5 mg | 10 mg |
| 50+ kg | 5 mg | 10 mg | 20 mg |

Each of these doses corresponds to the planned adult-equivalent dose based on the subject's weight.

Based on the protocol, each subject is randomized an adult-equivalent dose for the 28-day treatment period, which is captured in TRTxxP for ADSL and in TRTP for non-ADSL analysis data sets. But we still need to keep the actual dose level that the subject received, so how do we retain this information?

The statistical analysis plan (SAP) for this clinical trial specifies that safety and efficacy summaries will be performed based on the adult-equivalent dose *as it was taken*. The actual, adult-equivalent dose refers to the actual treatment arm and dose of Norteño that was administered to the subject during the course of the trial. Despite efforts to adhere to the protocol as much as possible, there may be deviations from the planned dose for various reasons, based on this specification to tabulate summaries based on actual dose, analysis data sets should therefore be structured such that TRTP/N and TRTA/N contain the adult-equivalent dose levels to facilitate analysis, wherein:

- 5 mg QD maps to the first column of summary tables;
- 10 mg QD maps to the second column of summary tables;
- 20 mg QD maps to the third column of summary tables.

A typical summary table may follow the table shell layout depicted in Table 2:

**Table 2 Mock Analysis Results Summary Table**

| | Adult-equivalent Dose of Norteño | | | | |
|---|---|---|---|---|---|
| | **5 mg QD (N=xx)** | **10 mg QD (N=xx)** | **20 mg QD (N=xx)** | **Total (N=xxx)** | **ADSL.TRT01A** |
| **Sex, n (%)** | | | | | **ADSL.SEX** |
| Male | xx (xx.x%) | xx (xx.x%) | xx (xx.x%) | xx (xx.x%) | |
| Female | xx (xx.x%) | xx (xx.x%) | xx (xx.x%) | xx (xx.x%) | |
| **Race, n (%)** | | | | | **ADSL.RACE** |
| White | xx (xx.x%) | xx (xx.x%) | xx (xx.x%) | xx (xx.x%) | |
| Asian | xx (xx.x%) | xx (xx.x%) | xx (xx.x%) | xx (xx.x%) | |
| Black or African American | xx (xx.x%) | xx (xx.x%) | xx (xx.x%) | xx (xx.x%) | |
| … | xx (xx.x%) | xx (xx.x%) | xx (xx.x%) | xx (xx.x%) | |
| **Age (years)** | | | | | **ADSL.AGE** |
| n | xx | xx | xx | xx | |
| mean (SD) | xx.x (xx.xx) | xx.x (xx.xx) | xx.x (xx.xx) | xx.x (xx.xx) | |
| min, max | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | |

The challenge arises in capturing the pediatric weight-adjusted dose within both subject-level and record-level data. To address this challenge, the trial can implement the following CDISC-defined treatment variables.

## TRTXXA/TRTXXP FALLS SHORT OF THE WEIGHT-ADJUSTED DOSE NEEDS

One consideration is to use TRTxxP and TRTP to contain the adult-equivalent dose while the TRTxxA and TRTA variables contain the pediatric weight-adjusted dose as the "actual" dose that the subjects were dispensed. This solution might have worked if everyone in the study received the protocol planned dose. If every subject took the study drug at the planned dose then all analyses could be performed on TRTP regardless of the SAP indicating actual dose because there would be no difference between the planned and actual adult-equivalent doses. Thus, perfect drug compliance allows us to use TRTP to capture the adult-equivalent and TRTA to capture the weight-adjusted dose.

**Table 3 CDISC ADSL Treatment Variables†**

| VARIABLE NAME | VARIABLE LABEL | TYPE | CODELIST / CT | CORE | CDISC NOTES |
|---|---|---|---|---|---|
| TRTxxP | Planned Treatment for Period xx | Char | | Req | Subject-level identifier that represents the planned treatment for period xx. In a one-period randomized trial, TRT01P would be the treatment to which the subject was randomized. TRTxxP might be derived from the SDTM DM variable ARM. At least TRT01P is required. |
| TRTxxPN | Planned Treatment for Period xx (N) | Num | | Perm | Subject-level identifier that represents the actual treatment dosage for period xx. |
| TRTxxA | Actual Treatment for Period xx | Char | | Cond | Subject-level identifier that represents the actual treatment for the subject for period xx. Required when actual treatment does not match planned and there is an analysis of the data as treated. |
| TRTxxAN | Actual Treatment for Period xx (N) | Num | | Perm | Numeric representation of TRTxxA. There must be a one-to-one relationship between TRTxxAN and TRTxxA within a study. TRTxxAN cannot be present unless TRTxxA is also present. When TRTxxA and TRTxxAN are present, then on a given record, either both must be populated or both must be null. |

(CDISC ADaM Team, 2021)

However, if one subject took something other than planned (e.g., Lilith was randomized to take the adult-equivalent of 10 mg QD equivalent, but actually took the adult-equivalent of 20 mg QD), then we need to use the TRTxxA/TRTA variables to capture the actual adult-equivalent instead of the weight-adjusted dose (see Table 4). This then causes a misstep in our dance and we need to quickly adjust our choreography to allow for this freestyle move.

† Table is copied directly from table 3.2.4 in section 3.2 in “Analysis Data Model Implementation Guide Version 1.3 (final)” published November 29, 2021.

**Table 4 Incomplete ADSL Data for Subjects in SPIN**

| SUBJID | WTBL | STRATAR | ARM | TRT01P | TRT01A |
|---|---|---|---|---|---|
| Subject ID | Baseline Weight (kg) | Strata Used for Randomization | Description of Planned Arm | Planned Treatment for Period 01 | Actual Treatment for Period 01 |
| Loki | 30 | 20 –< 35 kg | 5 MG NORTEÑO QD | 5 MG NORTEÑO QD | 5 MG NORTEÑO QD |
| Lilith | 25 | 20 –< 35 kg | 10 MG NORTEÑO QD | 10 MG NORTEÑO QD | 20 MG NORTEÑO QD |
| Chewy | 40 | 35 –< 50 kg | 20 MG NORTEÑO QD | 20 MG NORTEÑO QD | 20 MG NORTEÑO QD |
| Dot | 53 | 50+ kg | 10 MG NORTEÑO QD | 10 MG NORTEÑO QD | 10 MG NORTEÑO QD |

This excerpt from the ADSL data set is incomplete because additional variables are still required in order to capture the pediatric, weight-adjusted dose levels by subject and by record.

## INTRODUCING DOSEXXP/A

The CDISC ADaMIG v1.3 defines variables that can be added to ADSL to reflect the planned and actual pediatric, weight-adjusted dose levels for each pediatric subject. DOSExxP contains the planned pediatric weight-adjusted, while DOSExxA contains the actual pediatric weight-adjusted dose.

**Table 5 CDISC ADSL Dose Variables‡**

| VARIABLE NAME | VARIABLE LABEL | TYPE | CODELIST/ CT | CORE | CDISC NOTES |
|---|---|---|---|---|---|
| DOSExxP | Planned Treatment Dose for Period xx | Num | | Perm | Subject-level identifier that represents the planned treatment dosage for period xx. |
| DOSExxA | Actual Treatment Dose for Period | Num | | Perm | Subject-level identifier that represents the actual treatment dosage for period xx. |
| DOSExxU | Units for Dose for Period xx | Char | | Perm | The units for DOSExxP and DOSExxA. It is permissible to use suffixes such as "P" and "A" if needed, with labels modified accordingly. |

(CDISC ADaM Team, 2021)

In practice, the derivations for the DOSExxP/A variables may look something like the specifications shown in Table 6, where the planned, weight-adjusted dose (DOSE01P) is derived based on the randomized treatment group (TRT01P) and the weight-adjusted mapping provided by the sponsor in Table 1. The actual weight-adjusted dose (DOSE01A) is derived based on the exposure as collected – whether it is a collected field in an exposure clinical report form (CRF) or derived from tablet strength from drug accountability. In SPIN, SDTM exposure variables ECDOSE and EXDOSE reflect the adult-equivalent doses taken by subjects, and the pediatric weight-adjusted dose is collected in a CRF and stored in the supplemental exposure as collected SDTM variable WTDOSE. Whenever information is captured across more than one field in a database, it is good practice to cross-check that ECDOSE and WTDOSE are aligned as defined by their relationship in Table 1.

‡ Table is copied directly from table 3.2.5 in section 3.2 in “Analysis Data Model Implementation Guide Version 1.3 (final)” published November 29, 2021.

**Table 6 Excerpt from ADSL Variable Specifications for SPIN**

| VARIABLE NAME | VARIABLE LABEL | SOURCE | DERIVATION |
|---|---|---|---|
| DOSE01P | Planned Treatment Dose for Period 01 | Derived | Set to the numeric value of the pediatric dose level as mapped out in Table 1 for Weight-Based Pediatric Doses using the subject's weight used for randomization (DM.STRATAR) and the planned treatment (DM.ARM):<br>If DM.STRATAR = '20 –< 35 kg' perform the following: Set to 1 if DM.ARM = '5 MG NORTEÑO QD'; else set to 2.5 if DM.ARM = '10 MG NORTEÑO QD'; else set to 5 if DM.ARM = '20 MG NORTEÑO QD'.<br>Else if DM.STRATAR = '35 –< 50 kg' perform the following: Set to 2.5 if DM.ARM = '5 MG NORTEÑO QD'; else set to 5 if DM.ARM = '10 MG NORTEÑO QD'; else set to 10 if DM.ARM = '20 MG NORTEÑO QD'.<br>Else if DM.STRATAR = '50+ kg' perform the following: Set to 5 if DM.ARM = '5 MG NORTEÑO QD'; else set to 10 if DM.ARM = '10 MG NORTEÑO QD'; else set to 20 if DM.ARM = '20 MG NORTEÑO QD'. |
| DOSE01A | Actual Treatment Dose for Period 01 | Derived | Set to the numeric value of SUPPEC.WTDOSE.QVAL when matching records by USUBJID and ECSEQ |
| DOSE01U | Units for Dose for Period 01 | Assigned | Set to EC.ECDOSU |

The addition of these three variables allows reviewers to easily identify the randomized (adult-equivalent) treatment group for each subject as well as preserve the weight-adjusted pediatric doses that each subject received during this four-week treatment period.

**Table 7 ADSL Data for Subjects in SPIN**

| SUBJID | WTBL | STRATAR | ARM | TRT01P | TRT01A | DOSE01P | DOSE01A | DOSE01U |
|---|---|---|---|---|---|---|---|---|
| Subject ID | Baseline Weight (kg) | Strata Used for Randomization | Description of Planned Arm | Planned Treatment for Period 01 | Actual Treatment for Period 01 | Actual Treatment Dose for Period 01 | Actual Treatment Dose for Period 01 | Units for Dose for Period 01 |
| Loki | 30 | 20 –< 35 kg | 5 MG NORTEÑO QD | 5 MG NORTEÑO QD | 5 MG NORTEÑO QD | 1 | 1 | MG |
| Lilith | 25 | 20 –< 35 kg | 10 MG NORTEÑO QD | 10 MG NORTEÑO QD | 20 MG NORTEÑO QD | 2.5 | 5 | MG |
| Chewy | 40 | 35 –< 50 kg | 20 MG NORTEÑO QD | 20 MG NORTEÑO QD | 20 MG NORTEÑO QD | 10 | 10 | MG |
| Dot | 53 | 50+ kg | 10 MG NORTEÑO QD | 10 MG NORTEÑO QD | 10 MG NORTEÑO QD | 10 | 10 | MG |

As seen in Table 7, we now have the subject-level adult-equivalent and pediatric weight-based dose levels appropriately stored at the subject-level, let us move onto the next stanza of this choreographed DOSE-y DOE.

## BDS / OCCDS DATA SETS

As with ADSL, the variables TRTP and TRTA are sufficient in containing the planned and actual adult-equivalent doses, however, additional variables are needed to display the planned and actual weight-adjusted doses at each record level. The tables below display a subset of variables from the Adverse Events Analysis Dataset (ADAE), detailing the nine adverse events (AEs) collected for the four subjects during their enrollment in the SPIN study.

**Table 8 ADAE Data Set Excerpt with TRTP and TRTA for Subjects in SPIN**

| # | USUBJID | WTBL | STRATAR | TRTSDT | TRTEDT | TRTP | TRTA |
|---|---|---|---|---|---|---|---|
| | Subject ID | Baseline Weight (kg) | Strata Used for Randomization | Date of First Exposure to Treatment | Date of Last Exposure to Treatment | Planned Treatment | Actual Treatment |
| 1 | Chewy | 40 | 35 –< 50 kg | 2024-02-01 | 2024-02-28 | 20 MG NORTEÑO QD | 20 MG NORTEÑO QD |
| 2 | Chewy | 40 | 35 –< 50 kg | 2024-02-01 | 2024-02-28 | | |
| 3 | Dot | 53 | 50+ kg | 2024-02-01 | 2024-02-28 | 10 MG NORTEÑO QD | 10 MG NORTEÑO QD |
| 4 | Dot | 53 | 50+ kg | 2024-02-01 | 2024-02-28 | 10 MG NORTEÑO QD | 10 MG NORTEÑO QD |
| 5 | Dot | 53 | 50+ kg | 2024-02-01 | 2024-02-28 | 10 MG NORTEÑO QD | 10 MG NORTEÑO QD |
| 6 | Lilith | 25 | 20 –< 35 kg | 2024-02-01 | 2024-02-28 | 10 MG NORTEÑO QD | 20 MG NORTEÑO QD |
| 7 | Lilith | 25 | 20 –< 35 kg | 2024-02-01 | 2024-02-28 | 10 MG NORTEÑO QD | 20 MG NORTEÑO QD |
| 8 | Loki | 30 | 20 –< 35 kg | 2024-02-01 | 2024-02-28 | 5 MG NORTEÑO QD | 5 MG NORTEÑO QD |
| 9 | Loki | 30 | 20 –< 35 kg | 2024-02-01 | 2024-02-28 | 5 MG NORTEÑO QD | 5 MG NORTEÑO QD |

**Table 9 ADAE Data Set Excerpt with Adverse Event Variables for Subjects in SPIN**

| # | USUBJID | ASTDT | AENDT | AETERM |
|---|---|---|---|---|
| | Subject ID | Analysis Start Date | Analysis End Date | Adverse Event Reported Term |
| 1 | Chewy | 2024-02-01 | 2024-02-09 | RESTLESS LEG SYNDROME |
| 2 | Chewy | 2024-03-02 | 2024-03-31 | ELECTRICALLY SLIDING |
| 3 | Dot | 2024-02-03 | 2024-12-31 | POLKA DOTS |
| 4 | Dot | 2024-02-04 | 2024-02-05 | TWISTING AND SHOUTING |
| 5 | Dot | 2024-02-05 | 2024-02-12 | TWINKLE TOES |
| 6 | Lilith | 2024-02-01 | 2024-02-03 | JAZZ HANDS |
| 7 | Lilith | 2024-02-23 | 2024-02-26 | HUSTLING |
| 8 | Loki | 2024-02-01 | 2024-02-29 | DANCE FEVER |
| 9 | Loki | 2024-02-06 | 2024-02-08 | A LITTLE BOOGIE |

In order to ensure that the record-level data sets contain sufficient granularity to capture dose adjustments and deviations from the planned dose regimen accurately, we need to incorporate additional variables that contain information about the weight-adjusted doses. Commingling dosing variables into the analysis data sets is akin to adding a graceful pirouette to the routine in the analysis data sets to capture the weight-adjusted dose received by each subject at the record-level. In BDS and OCCDS data sets, the record-level pediatric weight-adjusted doses will be captured by DOSEP and DOSEA:

**Table 10 CDISC Record-Level Dose Variables for BDS Data Sets[§]**

| VARIABLE NAME | VARIABLE LABEL | TYPE | CODELIST/ CT | CORE | CDISC NOTES |
|---|---|---|---|---|---|
| DOSEP | Planned Treatment Dose | Num | | Perm | DOSEP represents the planned treatment dosage associated with the record. |
| DOSCUMP | Cumulative Planned Treatment Dose | Num | | Perm | Cumulative planned dosage of treatment for the subject at the point in time of the record (e.g., ADT). |
| DOSEA | Actual Treatment Dose | Num | | Perm | DOSEA represents the actual treatment dosage associated with the record. |
| DOSCUMA | Cumulative Actual Treatment Dose | Num | | Perm | Cumulative actual dosage of treatment for the subject at the point in time of the record (e.g., ADT). |
| DOSEU | Treatment Dose Units | Char | | Perm | The units for DOSEP, DOSCUMP, DOSEA, and DOSCUMA. It is permissible to use suffixes such as "P" and "A" if needed, with labels modified accordingly. |

(CDISC ADaM Team, 2021)

Incorporating these dosing variables enables the preservation and analysis of dose-related information within the analysis data set. Table 11 illustrates possible variable definitions and derivations within the metadata when integrating the DOSEP and DOSEA variables into a non-ADSL dataset.

**Table 11 ADAE Metadata for SPIN**

| VARIABLE NAME | VARIABLE LABEL | TYPE | LENGTH | SOURCE | DERIVATION |
|---|---|---|---|---|---|
| USUBJID | Unique Subject Identifier | Char | 6 | AE.USUBJID | |
| TRTP | Planned Treatment for Period 01 | Char | 16 | DM.ARM | Set to ADSL.TRT01P if TRTSDT <= ASTDT <= TRTEDT + 1 day. |
| TRTA | Actual Treatment for Period 01 | Char | 16 | Derived | Set to ADSL.TRT01A if TRTSDT <= ASTDT <= TRTEDT + 1 day. |
| DOSEP | Planned Treatment Dose for Period 01 | Num | 8 | Derived | Set to ADSL.DOSE01P if TRTSDT <= ASTDT <= TRTEDT + 1 day. |
| DOSEA | Actual Treatment Dose for Period 01 | Num | 8 | Derived | Set to ADSL.DOSE01A if TRTSDT <= ASTDT <= TRTEDT + 1 day. |
| DOSEU | Units for Dose for Period 01 | Char | 2 | Assigned | Set to ADSL.DOSE01U if TRTSDT <= ASTDT <= TRTEDT + 1 day. |

[§] Table is copied directly from table 3.3.2.2 in section 3.3 in “Analysis Data Model Implementation Guide Version 1.3 (final)” published November 29, 2021.

The SPIN clinical trial was designed with one treatment period where the subjects are expected to receive a constant dose of Norteño for 28 days. In this trial, the analysis period includes the Treatment Period (start of treatment to end of treatment) as well as 1-day post-treatment. This analysis period is used to determine the values of DOSEP and DOSEA per record (as defined in Table 11). Now, if we imagine a more intricate clinical trial with multiple treatment periods, imagine it as a choreographed routine. Each analysis period, represented by the APERIOD/C variables, determines the values assigned to TRTP, TRTA, DOSEP, and DOSEA because these four treatment and dose variables are constant within each subject's treatment period. Table 12 illustrates the use of DOSEP, DOSEA and DOSEU for each record.

**Table 12 ADAE Data Set Excerpt with DOSEP and DOSEA for Subjects in SPIN**

| # | USUBJID | DOSEP | DOSEA | DOSEU | ASTDT | AENDT | AETERM |
|---|---|---|---|---|---|---|---|
| | Subject ID | Planned Treatment Dose | Actual Treatment Dose | Treatment Dose Units | Analysis Start Date | Analysis End Date | Adverse Event Reported Term |
| 1 | Chewy | **10** | **10** | **MG** | 2024-02-01 | 2024-02-09 | RESTLESS LEG SYNDROME |
| 2 | Chewy | | | | 2024-03-02 | 2024-03-31 | ELECTRICALLY SLIDING |
| 3 | Dot | **10** | **10** | **MG** | 2024-02-03 | 2024-12-31 | POLKA DOTS |
| 4 | Dot | **10** | **10** | **MG** | 2024-02-04 | 2024-02-05 | TWISTING AND SHOUTING |
| 5 | Dot | **10** | **10** | **MG** | 2024-02-05 | 2024-02-12 | TWINKLE TOES |
| 6 | Lilith | **2.5** | **5** | **MG** | 2024-02-01 | 2024-02-03 | JAZZ HANDS |
| 7 | Lilith | **2.5** | **5** | **MG** | 2024-02-23 | 2024-02-26 | HUSTLING |
| 8 | Loki | **1** | **1** | **MG** | 2024-02-01 | 2024-02-29 | DANCE FEVER |
| 9 | Loki | **1** | **1** | **MG** | 2024-02-06 | 2024-02-08 | A LITTLE BOOGIE |

Still, this is not enough to adequately capture the natural weight fluctuations and dose adjustments that occur during clinical trials. Enter stage left, DOSEON.

## DOSEON

DOSEON is a dosing variable that was first introduced to occurrence data sets in ADaM OCCDS v1.1, but its use may be considered for any non-ADSL analysis dataset. DOSEON and its related dosing variables are introduced by the ADaM OCCDS as, "The treatment variable used for analysis must be included. Typically, this would be TRTP, TRTA, TRTxxP, or TRTxxA. … Additional dosing variables may also be included." (CDISC ADaM Team, 2016) And then proceeds to define the following variables.

**Table 13 ADAM Treatment/Dose Variables**[**]

| VARIABLE NAME | VARIABLE LABEL | TYPE | CODELIST | CONTROLLED TERMS | SUBCLASS ADVERSE EVENT CORE | CDISC NOTES |
|---|---|---|---|---|---|---|
| DOSEON | Treatment Dose at Record Start | Num | | | Perm | Dose received at the point in time of the record start date Example derivation: Obtained from EX.EXDOSE where --STDTC falls between the values of EX.EXSTDTC and EX.EXENDTC |
| DOSCUMA | Cumulative Actual Treatment Dose | Num | | | Perm | Cumulative actual study drug dosage at the point in time of the record start date |
| DOSEU | Treatment Dose Units | Char | (UNIT)[††] | | Perm | The units associated with DOSEON and/or DOSCUMA. Conditional on whether DOSEON and/or DOSCUMA are included. |

(CDISC ADaM Team, 2016)

DOSEON stands out on the CDISC ADaM dance floor for its unique flair – it contains the dose at the record start date, which differs from DOSEP and DOSEA which contain the planned/actual dose for the treatment period, which is not expected to change with time (or with another pre-specified variable). As such, DOSEON is nimble enough to capture nuances in dose changes over time. This flexibility proves invaluable in capturing dose variations caused by factors like changes in weight, as is common with longitudinal studies where weights may be expected to change, or in clinical trials where the dose level of the drug are allowed to be adjusted for safety.

**Table 14 ADAE Metadata**

| VARIABLE NAME | VARIABLE LABEL | SOURCE | DERIVATION |
|---|---|---|---|
| DOSEON | Treatment Dose at Record Start | Derived | Obtained from EX.EXDOSE: if ASTDT falls between the values of EX.EXSTDTC and EX.EXENDTC then set to EX.EXDOSE (inclusive); otherwise set to last dose taken prior to ASTDT. |

[**] Table is copied directly from table 3.2.7.1 in section 3.2 in "Analysis Structure for Occurrence Data (OCCDS) Version 1.0" published February 12, 2016.
[††] Note: Codelists in parenthesis are the names of CDISC Controlled Terminology

For example, in SPIN, Dot debuts the clinical trial with two AEs: polka dots immediately followed by twisting and shouting. After the onset of the serious event of twisting and shouting, the SPIN medical monitor made the safe decision to decrease Dot's pediatric weight-adjusted dose by 2 mg. Thus, while Dot was randomized to the 10 mg Norteño QD treatment group and Dot received 10 mg per her weight-adjusted dose, she was titrated down to 8 mg Norteño QD on February 5th and therefore was receiving 8 mg at the onset of her third AE of twinkle toes. This information is captured in DOSEON which is information that would not have otherwise been retained by DOSEP or DOSEA (refer to Table 15).

**Table 15 ADAE Data Set Excerpt with DOSEP, DOSEA, and DOSEON**

| # | USUBJID | DOSEP | DOSEA | DOSEON | DOSEU | ASTDT | AENDT | AETERM |
|---|---|---|---|---|---|---|---|---|
| | Subject ID | Planned Treatment Dose | Actual Treatment Dose | Treatment Dose at Record Start | Treatment Dose Units | Analysis Start Date | Analysis End Date | Adverse Event Reported Term |
| 1 | Chewy | 10 | 10 | 10 | MG | 2024-02-01 | 2024-02-09 | RESTLESS LEG SYNDROME |
| 2 | Chewy | | | 10 | | 2024-03-02 | 2024-03-31 | ELECTRICALLY SLIDING |
| 3 | Dot | 10 | 10 | 10 | MG | 2024-02-03 | 2024-12-31 | POLKA DOTS |
| 4 | Dot | 10 | 10 | 10 | MG | 2024-02-04 | 2024-02-05 | TWISTING AND SHOUTING |
| 5 | Dot | 10 | 10 | 8 | MG | 2024-02-05 | 2024-02-12 | TWINKLE TOES |
| 6 | Lilith | 2.5 | 5 | 5 | MG | 2024-02-01 | 2024-02-03 | JAZZ HANDS |
| 7 | Lilith | 2.5 | 5 | 5 | MG | 2024-02-23 | 2024-02-26 | HUSTLING |
| 8 | Loki | 1 | 1 | 1 | MG | 2024-02-01 | 2024-02-29 | DANCE FEVER |
| 9 | Loki | 1 | 1 | 1 | MG | 2024-02-06 | 2024-02-08 | A LITTLE BOOGIE |

## CONCLUSION

The SPIN clinical trial illustrates the complexity of capturing dosing levels in pediatric populations, where doses often sway with individual body sizes, requiring adjustments to stay in sync with each participant's unique weight. By incorporating subject-level and record-level variables to capture weight-adjusted doses, the trial can maintain fluidity and granularity necessary for comprehensive understanding of the subject's dosing pattern, all while adhering to the structured beat of CDISC standards for data organization and reporting.

CDISC ADaM data structures, including ADSL, BDS, and OCCDS, represent standardized frameworks, providing a common stage for organizing, formatting, and analyzing clinical trial data within the CDISC ecosystem. Adherence to CDISC standards not only benefits sponsors, regulators, and researchers but also ultimately serves the interests of patients by fostering transparency, consistency, and reliability in clinical research data. By promoting the adoption of these standards across the industry, CDISC continues to lead the choreography in advancing the efficiency, integrity, and impact of clinical research worldwide.

## REFERENCES

CDISC ADaM Team. (2009, December 7). *ADaM v2.1*. Retrieved April 2, 2024, from CDISC: https://www.cdisc.org/standards/foundational/adam/adam-v2-1

CDISC ADaM Team. (2016, February 12). *ADaM Structure for Occurrence Data Implementation Guide v1.1*. Retrieved April 2, 2024, from CDISC: https://www.cdisc.org/standards/foundational/adam/adam-structure-occurrence-data-implementation-guide-v1-1

CDISC ADaM Team. (2021, November 29). *ADaMIG v1.3*. Retrieved March 26, 2024, from CDISC: https://www.cdisc.org/standards/foundational/adam/adamig-v1-3

CDISC Website. (2024). *Standards*. Retrieved April 2, 2024, from CDISC: https://www.cdisc.org/standards

ICH Expert Working Group. (1995, November 30). Structure and Content of Clinical Study Reports E3. *ICH Harmonised Tripartite Guideline, 3*. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Retrieved from https://database.ich.org/sites/default/files/E3_Guideline.pdf

Watson, R. (2022). CDISC ADaM Implementation by Example. DataRich Consulting.

Acknowledgments

## CONTACT INFORMATION

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

Inka Leprince
PharmaStat, LLC
ileprince@pharmastat.com

Richann Jean Watson
DataRich Consulting
richann.watson@datarichconsulting.com