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Design Considerations for ADaM Protocol Deviations Dataset in Vaccine Studies

Rashmi Gundaralahalli Ramesh, Merck & Co., Inc ., Rahway, NJ, USA;
Jeffrey Lavenberg, Merck & Co., Inc ., Rahway, NJ, USA

ABSTRACT

Per-protocol analysis of immunogenicity data in vaccine trials is essential for evaluating efficacy. The ADaM dataset for protocol deviations (ADPDEV) is critical in excluding samples with clinically important protocol deviations from the analysis. However, challenges arise in determining the impact of deviations in studies with multiple doses and concomitant vaccinations, which require different exclusion rules. For instance, the same deviation term may lead to participant level exclusions or visit level exclusions. If there are multiple concomitant vaccinations, then each vaccination may follow a different rule to qualify for exclusion at each visit.

This paper focuses on creating ADPDEV dataset in vaccine studies, specifically addressing studies with multiple doses and/or concomitant vaccinations. We present a systematic approach for determining sample exclusions based on the nature and timing of protocol deviations. The list of protocol deviations received from the clinical team is used as input for the SDTM deviations (DV) dataset, which in turn is used to create ADPDEV. By following the ADaM Occurrence Data Structure (OCCDS) structure, the ADPDEV dataset is constructed to capture one record per subject, per violation, per timepoint, per assay. To accurately identify immunogenicity results corresponding to protocol deviations, we merge the ADPDEV dataset with the analysis dataset for immunogenicity (ADIMM) and derive a per-protocol record level flag (PPROTRFL).

Our findings emphasize the importance of defining the exclusion rules based on the protocol deviations and timing. We demonstrate the programming challenges and significance of accurately constructing the ADPDEV dataset to ensure robust per-protocol analysis in vaccine studies.

1. INTRODUCTION

Vaccine clinical trials are conducted to evaluate the safety and immunogenicity of novel vaccines and hence play a vital role in public health. These studies require meticulous adherence to study protocols to ensure valid and reliable results. However, protocol deviations inevitably occur due to various factors such as participant non-compliance and unforeseen circumstances in clinical trial operations. The accurate identification and handling of protocol deviations that may interfere with the evaluation of immune response are crucial for maintaining data integrity and effectively analyzing immunogenicity data in vaccine trials.

To facilitate protocol deviation analyses in a systematic manner, an analysis dataset needs to be created which is then used for immunogenicity analyses. CDISC Analysis Data Model (ADaM) defines the fundamental principles and standards to follow in the creation of analysis datasets and associated metadata. The analysis dataset for protocol deviation (ADPDEV) follows ADaM Occurrence data structure (OCCDS). Occurrence analysis is the counting of subjects with a given record or term, and often includes a structured hierarchy of dictionary coding categories [1]. This dataset contains records for specific participants and visits that are considered to have important protocol deviations. These deviations can be any actions or events that do not comply with the study protocol and lead to samples inappropriate for analysis. When protocol deviations impact only certain participants and/or visits, it is necessary to exclude the corresponding data from the per-protocol analysis of immunogenicity data.

The primary objective of this paper is to provide details of the critical aspects involved in the design and implementation of the ADaM Protocol Deviations dataset. Through detailed examples, code snippets, and data snapshots, this paper aims to assist statistical programmers and statisticians in effectively identifying and recording protocol deviations in a systematic and compliant manner.

The structure of this paper is organized in a manner that the first section discusses the study design considerations, followed by structure of ADPDEV, general considerations, and challenges associated with identifying participant level and visit level protocol deviations. Lastly, the paper concludes by highlighting the potential impact of a well-designed dataset on the accurate analysis and interpretation of vaccine study results.

2. VACCINE STUDY DESIGN CONSIDERATIONS

In evaluating the immunogenicity of vaccines through clinical trials, the study design is of paramount importance. This process, which requires a collaborative effort from a multi-disciplinary team, necessitates attention to a variety of factors that can interfere with valid and reliable results. This involves consideration for protocol deviations (PDs) and protocol violations (PVs) that can impact the desired immune response.

Key aspects, such as Screening and Randomization, as well as scheduling of visits, administering study and concomitant vaccines, and conducting blood draws and assays, can be subject to PDs and PVs, which if not properly managed, can compromise the study's findings. For instance, immunogenicity is gauged using antibodies present in the participants' serum samples. Several factors including the number of administered doses, interval between vaccinations and timing of serum collection after the final dose can influence antibody concentration. PDs related to these elements, such as missed doses or irregular serum collection timing, could interfere with the accurate assessment of vaccine immunogenicity, necessitating exclusion of such samples from analysis. Furthermore, post-dose visits are instrumental in tracking long-term immunogenicity. PDs related to these visits may skew data, bringing into question the vaccine's long-term effects.

With careful planning and adherence to the protocol, researchers can navigate PDs and PVs, ensuring effective data collection and accurate evaluation of vaccine safety and immunogenicity. The focus on PDs and PVs brings to the forefront the importance of rigorous study design and strict protocol adherence in assessing a vaccine's performance.

Table 1 shows a sample study design that will be used to illustrate different scenarios that may lead to important protocol deviations that could impact the immunogenicity analyses.

	Visit 1 Day 1	**Visit 2 Day 180**	**Visit 3 30 Days Post SV Dose 2**	**Visit 4 Day 270**	**Visit 5 30 Days Post SV Dose 3**
Initial Activity	Screening Informed Consent Randomization		Blood draw	Blood draw[a]	Blood draw
Study Vaccine	SV Dose 1	SV Dose 2		SV Dose 3	
Concomitant Vaccine	CV1 Dose 1	CV1 Dose 2		CV2 Dose 1 CV3 Dose 1	

[a] Serology samples for SV analyses were to be collected at Visit 4 prior to vaccination.

CV1=Concomitant Vaccine 1; CV2=Concomitant Vaccine 2; CV3=Concomitant Vaccine 3; PD=Postdose; SV=Study Vaccine.

Table 1. Sample study design.

3. STRUCTURE OF ADPDEV

The ADaM Protocol Deviations dataset (ADPDEV) is organized according to the ADaM Occurrence Data Structure (OCCDS). The ADPDEV dataset captures one record for each protocol deviation at the subject level, visit level, and assay level. Each of these individual records is then time-stamped to precisely capture the timing of the protocol deviations. The structure of the ADPDEV dataset allows for a meticulous capture of deviations, enabling a thorough analysis of how these deviations may have affected the immunogenicity results.

Referencing the OCCDS Implementation Guide v1.1, some important variables in the ADPDEV dataset are shown in Table 2 (below)

Variable Name (Label)	Description
STUDYID (Study Identifier)	Identifies the study for which the dataset has been created.
USUBJID (Unique Subject Identifier)	An identifier that is unique for each subject across all studies.
ASTDT (Analysis Start Date)	Date when the protocol deviation started.
ATERM (Analysis Term)	A brief, non-standardized term or phrase describing the protocol deviation.
ADECOD (Analysis Standardized Term)	A standardized term for the protocol deviation, generally derived from value-level metadata.
ADECODN (Analysis Standardized Term (N))	A numerical representation of the standardized term for protocol deviations, which can be useful for sorting purposes.
ACAT1 (Analysis Category 1)	Category or type of the protocol deviation. It groups similar protocol deviations together for simplified analysis.
ACAT2 (Analysis Category 2)	An additional category or type of protocol deviation, which provides more granularity to the protocol deviation characterization.
ACAT2N (Analysis Category 2 (N))	A numerical representation of the second category of protocol deviations, which can be used for sorting purposes.
AVISIT (Analysis Visit)	Name or description of the analysis visit when the protocol deviation occurred.
AVISITN (Analysis Visit (N))	Numeric representation of the analysis visit when the protocol deviation occurred, useful for sorting purposes.
SRCDOM (Source Data)	The name of the domain (dataset) that is the source of the data for the analysis (e.g., “DV”,”IS”)
SRCSEQ (Source Sequence Number)	The unique number assigned to each record in a domain dataset, which helps to identify the data's origin in the source dataset (e.g., 1, 15).

Table 2. Important variables in ADPDEV

Different scenarios will require different exclusion rules within the ADPDEV. For instance, a study may have multiple samples collected before and after each vaccination. If a participant misses a scheduled vaccination or receives a vaccination outside the specified window, it could lead to the exclusion of samples collected after the vaccination time but not the samples collected prior to it.

To accommodate these nuances, the ADPDEV dataset is designed to be flexible and comprehensive. Its structure allows for the inclusion of information that is specific to studies with different dosing schedules and concomitant vaccinations. In addition, having ADPDEV “analysis ready” makes it simple to create tables which summarize the exclusions due to important protocol deviations.

4. CREATION OF ADPDEV DATASET FOR VACCINE STUDIES

This section addresses the handling of participant and visit level exclusions by providing brief description of few typical scenarios from vaccine studies. The code snippets that can be used to derive these exclusions is also provided along with the data snapshots. SAS programming challenges and code snippets for some exclusions involving complex algorithms are also discussed.

4.1. DERIVATION OF PARTICIPANT LEVEL EXCLUSIONS

	Analyses for SV			Analyses for CV1	Analyses for CV2/CV3
Exclusion	**Visit 3 (30 Days PD2)**	**Visit 4[a] (Day 270)**	**Visit 5 (30 Days PD3)**	**Visit 3 (30 Days PD2)**	**Visit 5 (30 Days PD3)**
Participant-level exclusion	E	E	E	E	E

[a] Serology samples for SV analyses were to be collected at Visit 4 prior to vaccination.
CV1=Concomitant Vaccine 1; CV2=Concomitant Vaccine 2; CV3=Concomitant Vaccine 3; E=Exclude; PD=Postdose; SV=Study Vaccine.

Table 3. Example criteria for participant-level exclusion

Participant level exclusion causes all data from a given participant to be excluded from per-protocol population analyses as shown in Table 3. In our implementation, ADPDEV has all the visits with immunogenicity blood draw for these participants. The per-protocol flag (PPROTRFL) is derived in immunogenicity analysis dataset (ADIMM) using ADPDEV to flag the records used for per-protocol analysis. Here are some examples for participant level exclusion. The participants with these deviation(s) will not be included in any Tables, Listings and Figures (TLFs) for per-protocol population.

1. Participant had no documented consent to enter the trial: Here is a sample code for the macro used for participant level exclusion reasons to exclude samples collected at all scheduled time points (30 days after Dose 2 at Visit 3, 30 days after Dose 3 at Visit 5, and Prior to Dose 3 at Visit 4). Using this macro in a data step, ADPDEV stores information on the deviation description (ADECOD), the time points of exclusion (AVISIT), exclusion type (ACAT2) and its higher category (ACAT1) for this specific Protocol deviation – see Table 4.

```
/*Participant level exclusion*/

%macro parlvl;
  ACAT1= 'Immunogenicity Category 1';
  avisit='30 Days Postdose 2'; avisitn=3; output;
  avisit='Prior to Dose 3';    avisitn=4; output;
  avisit='30 Days Postdose 3'; avisitn=5; output;

  ACAT1='Immunogenicity Category 2';
  avisit='30 Days Postdose 2'; avisitn=3; output;
  avisit='Prior to Dose 3';    avisitn=4; output;
  avisit='30 Days Postdose 3'; avisitn=5; output;

  ACAT1='Concomitant vaccine 1';
  avisit='30 Days Postdose 2';avisitn=3;output;
  avisit='30 Days Postdose 3'; avisitn=5;

  ACAT1='Concomitant vaccine 2';output;
  ACAT1='Concomitant vaccine 3';output;
%mend parlvl;
```

USUBJID	ADECOD	ACAT1	ACAT2	AVISIT
abc-0002	Not consented	Immunogenicity Category 1	Participant-level exclusions	30 Days Postdose 2
abc-0002	Not consented	Immunogenicity Category 1	Participant-level exclusions	Prior to Dose 3

abc-0002	Not consented	Immunogenicity Category 1	Participant-level exclusions	30 Days Postdose 3
abc-0002	Not consented	Immunogenicity Category 2	Participant-level exclusions	30 Days Postdose 2
abc-0002	Not consented	Immunogenicity Category 2	Participant-level exclusions	Prior to Dose 3
abc-0002	Not consented	Immunogenicity Category 2	Participant-level exclusions	30 Days Postdose 3
abc-0002	Not consented	Concomitant vaccine 1	Participant-level exclusions	30 Days Postdose 2
abc-0002	Not consented	Concomitant vaccine 2	Participant-level exclusions	30 Days Postdose 3
abc-0002	Not consented	Concomitant vaccine 3	Participant-level exclusions	30 Days Postdose 3

Table 4. ADPDEV dataset example with important variables for one participant

2. Failure to receive Study vaccine doses – When a participant fails to receive the study vaccine(s) 1 or 2, the immunogenicity results are excluded from the per-protocol analysis. As illustrated in Table 5, if a participant misses Dose 1 or 2 of the study vaccine (Scenario # 1 and 2), all data from this participant will be excluded from the per-protocol population (indicated by "E") resulting in participant level exclusion, which can be handled using the participant level exclusion macro shown above in (1).

Scenario #	Time of Deviation	Analyses for Response to SV			Analyses for Response to CV1	Analyses for Response to CV2/CV3
		Visit 3 (30 Days PD2) Blood draw	Visit 4[a] (Day 270) Blood draw	Visit 5 (30 Days PD3) Blood draw	Visit 3 (30 Days PD2)	Visit 5 (30 Days PD3)
	Failure to receive SV					
1	At Visit 1	E	E	E	E	E
2	At Visit 2	E	E	E	E	E
3	At Visit 4	I	I	E	I	E
	Failure to receive CV1					
4	At Visit 1	E	I	I	E	I
5	At Visit 2	E	I	I	E	I
	Failure to receive CV2/CV3					
6	At Visit 4	I	I	E	I	E
	[a] Serology samples for SV analyses were to be collected at Visit 4 prior to vaccination. CV1=Concomitant Vaccine 1; CV2=Concomitant Vaccine 2; CV3=Concomitant Vaccine 3; E=Exclude; I=Include (do not exclude); PD=Postdose; SV=Study Vaccine.					

Table 5. Exclusion criteria example for missed dose(s)

```
/* Failure to receive Study vaccine */

data miss_ex;
   set miss_ex12; /*Participants who missed Doses 1,2*/

   adecod='Missed at least one study vaccination at Vaccination 1, 2';
   adecodn=12;
   acat2="Participant-level exclusions"; acat2n=1;

   acat1='Immunogenicity Category 1';
   avisit='30 Days Postdose 2'; avisitn=3; output;
   avisit='Prior to Dose 3';    avisitn=4; output;
   avisit='30 Days Postdose 3'; avisitn=5; output;

   acat1='Immunogenicity Category 2';
   avisit='30 Days Postdose 2'; avisitn=3; output;
   avisit='Prior to Dose 3';    avisitn=4; output;
   avisit='30 Days Postdose 3'; avisitn=5; output;
```

```
   acat1='Concomitant vaccine 1';
   avisit='30 Days Postdose 2'; avisitn=3; output;

   avisit='30 Days Postdose 3'; avisitn=5;
   acat1='Concomitant vaccine 2'; output;
   acat1='Concomitant vaccine 3'; output;
run;
```

USUBJID	ADECOD	ACAT1	ACAT2	AVISIT
abc-0021	Missed at least one study vaccination at Vaccination 1, 2	Immunogenicity Category 1	Participant-level exclusions	30 Days Postdose 2
abc-0021	Missed at least one study vaccination at Vaccination 1, 2	Immunogenicity Category 1	Participant-level exclusions	Prior to Dose 3
abc-0021	Missed at least one study vaccination at Vaccination 1, 2	Immunogenicity Category 1	Participant-level exclusions	30 Days Postdose 3
abc-0021	Missed at least one study vaccination at Vaccination 1, 2	Immunogenicity Category 2	Participant-level exclusions	30 Days Postdose 2
abc-0021	Missed at least one study vaccination at Vaccination 1, 2	Immunogenicity Category 2	Participant-level exclusions	Prior to Dose 3
abc-0021	Missed at least one study vaccination at Vaccination 1, 2	Immunogenicity Category 2	Participant-level exclusions	30 Days Postdose 3
abc-0021	Missed at least one study vaccination at Vaccination 1, 2	Concomitant vaccine 1	Participant-level exclusions	30 Days Postdose 2
abc-0021	Missed at least one study vaccination at Vaccination 1, 2	Concomitant vaccine 2	Participant-level exclusions	30 Days Postdose 3
abc-0021	Missed at least one study vaccination at Vaccination 1, 2	Concomitant vaccine 3	Participant-level exclusions	30 Days Postdose 3

Table 6. Few rows from ADPDEV showing participant level exclusion due to missed dose(s)

3. Received Incorrect treatment – This is a participant level exclusion for first dose and visit level exclusion for later doses after protocol violation. If a participant was dispensed study intervention other than what was assigned in the allocation schedule, i.e. incorrect medication or potential cross-treatment for the first dose then the participant is excluded from the per-protocol population for all immunogenicity analyses. The participant level exclusion can be handled in similar manner as the above in section 4.1.1.

4.2 DERIVATION OF VISIT LEVEL EXCLUSIONS

Visit level protocol exclusions cause only data for specific visits from a given participant to be excluded from per-protocol population analyses. In our implementation, ADPDEV will have only impacted visits with immunogenicity blood draw for these participants. The per-protocol flag (PPROTRFL) is derived using ADPDEV to flag the records in immunogenicity analysis dataset corresponding to these participants and visits. The specific visits impacted by these deviation(s) will not be included in per-protocol analysis. Here are some examples for visit level exclusions.

1. Blood draw out of window –This refers to a deviation from the protocol-defined visit window of blood draw. If blood samples are collected outside of this window, the immunogenicity results from those samples will be excluded. To determine which specific immunogenicity results are excluded, timing of the deviation needs to be considered. For instance, if the protocol states that blood draw should occur between 26 to 43 days after vaccination, the dates of exposure to vaccination for each vaccine should be obtained from the SDTM.EX dataset, and the dates of blood draw at each visit should be obtained from the SDTM.IS dataset. Then, the difference between the exposure and blood draw dates should be checked at each visit. If the difference is not between 26 to 43 days, the immunogenicity results for that visit should be excluded from the per-protocol population. If the difference is less than 26 or greater than 43 for a particular visit, it indicates that the blood draw was either too early or too late, and the results are considered unreliable. Below is a sample code illustrating this process, and Table 7 provides a snapshot of the data with excluded visits.

```
%*--- Get dates of Visit3, Visit5 from IS as avisit3 and avisit5 ---*;

%*--- Get dates of Visit2, Visit4 from EX as visit2 and visit4 ---*;
```

```
data row1;
  set ex_is;
  if missing(avisit3) ne 1 and missing(visit2) ne 1 then d_pd2 = avisit3-visit2+1;
  if missing(avisit5) ne 1 and missing(visit4) ne 1 then d_pd3 = avisit5-visit4+1;
  ADECOD ="Blood Draw Out of Window Days 26-43";
  ADECODN = 33;
  acat3='Trial Procedures';
  acat3n=6;
  if missing(avisit3) ne 1 and (.<d_pd2<26 or d_pd2>43) then do;
      avisit='30 Days Postdose 2'; avisitn=3;acat2="Visit-level exclusions -  Visit
3";acat2n=2;
      ACAT1='Immunogenicity Category 1';output;
      ACAT1='Immunogenicity Category 2';output;
  end;
  if missing(avisit5) ne 1 and (.<d_pd3<26 or d_pd3>43) then do;
    avisit='30 Days Postdose 3'; avisitn=5; acat2="Visit-level exclusions - Visit 5";
    acat2n=4;
    ACAT1='Immunogenicity Category 1';output;
    ACAT1='Immunogenicity Category 2';output;
  end;
run;
```

USUBJID	ADECOD	ACAT1	ACAT2	AVISIT
abc-1234	Blood Draw Out of Window Days 26-43	Immunogenicity Category 1	Visit-level exclusions - Visit 3	30 Days Postdose 2
abc-1234	Blood Draw Out of Window Days 26-43	Immunogenicity Category 2	Visit-level exclusions - Visit 3	30 Days Postdose 2
abc-1278	Blood Draw Out of Window Days 26-43	Immunogenicity Category 1	Visit-level exclusions - Visit 5	30 Days Postdose 3
abc-1278	Blood Draw Out of Window Days 26-43	Immunogenicity Category 2	Visit-level exclusions - Visit 5	30 Days Postdose 3

Table 7. Snapshot of important variables from ADPDEV for Blood draw out of window

2. Missing serology results – If the immunogenicity assay does not generate valid result or samples are not collected, valid results are missing in the SDTM.IS dataset and this information can be stored in the ADPDEV dataset with ADECOD set to "Missing serology results" for the specific visit.

3. Failure to receive Study vaccine dose 3 or concomitant vaccine 1/2/3 – If a participant misses Study vaccine Dose 3 at Visit 4 (scenario #3 in Table 5), it is a visit level exclusion and excludes test results collected after Visit 4 (i.e., assay measuring the response to the study vaccine at Visit 5 and the assay results for responses for Concomitant vaccines 2 and 3 at Visit 5). Notably, the analysis for test results assessing the immune response to concomitant vaccine 1 at Visit 3 will still be included (indicated by "I"). Also, the missed dose of concomitant vaccine 1 at Visit 1 or 2 will result in exclusion of analyses of responses to concomitant vaccine and study vaccine at Visit 3. The missed dose of concomitant vaccines 2 or 3 will only lead to exclusion of analyses of concomitant vaccine 2 or 3 and study vaccine at Visit 5 as shown in Table 5. Below is a sample code and the important variables in ADPDEV – see Table 8. Using this macro, ADPDEV stores information on the deviation description (ADECOD), the time points of exclusion (AVISIT), exclusion type (ACAT2) and its higher category (ACAT1). ACAT1 distinguishes assay type, corresponding to vaccine types, such as SV, CV1, or CV2 for this specific protocol deviation.

```
data miss_ex;
   set miss_ex3; /*Participants who missed Dose 3*/

   adecod='Missed study vaccination at Vaccination 3';
   adecodn=13;
   avisit='30 Days Postdose 3'; avisitn=5;acat2="Visit-level exclusions - Visit 5"; acat2n=4;

   /* Code continued from previous page */

   acat1='Immunogenicity Category 1'; output;
   acat1='Immunogenicity Category 2'; output;
   acat1='Concomitant vaccine 2'; output;
   acat1='Concomitant vaccine 3'; output;
run;
```

```
/* Failure to receive concomitant vaccine 1 */

  data miss_cv1;
    length avisit $30 acat1 acat2 $100 adecod $150;
    set miss_exp; /*Participants who missed concomitant vaccine 1*/
    adecod='Missed at least one dose of CV1 at Vaccination 1, 2';
    adecodn=25;
    acat2="Visit-level exclusions - Visit 3";
    acat2n=2;
    avisit='30 Days Postdose 2'; avisitn=3;
    acat1='Immunogenicity Category 1';output;
    acat1='Immunogenicity Category 2';output;
    acat1='Concomitant vaccine 1';output;
  run;

/* Failure to receive concomitant vaccine 2/3 */

 data miss_cv23;
    length avisit $30 acat1 acat2 $100 adecod $150;
    set miss_ex23;  /*Participants who missed concomitant vaccine 2 or 3*/
    acat2="Visit-level exclusions - Visit 5";
    acat2n=4;
    avisit='30 Days Postdose 3'; avisitn=5;acat2="Visit-level exclusions - Visit 5"; acat2n=4;
    if exspid = "Concomitant vaccine 2" then do;/*If concomitant vaccine 2 is missed*/
        adecod='Missed Concomitant vaccine 2 at Vaccination 3';
       acat1='Immunogenicity Category 1';output;
       acat1='Immunogenicity Category 2';output;
       acat1='Concomitant vaccine 2';output;
    end;
    if exspid = "Concomitant vaccine 3" then do;/*If concomitant vaccine 3 is missed*/
        adecod='Missed Concomitant vaccine 3 at Vaccination 3';
       acat1='Immunogenicity Category 1';output;
       acat1='Immunogenicity Category 2';output;
       acat1='Concomitant vaccine 3';output;
    end;
run;
```

USUBJID	ADECOD	ACAT1	ACAT2	AVISIT
abc-0022	Missed study vaccination at Vaccination 3	Immunogenicity Category 1	Visit-level exclusions - Visit 5	30 Days Postdose 3
abc-0022	Missed study vaccination at Vaccination 3	Immunogenicity Category 2	Visit-level exclusions - Visit 5	30 Days Postdose 3
abc-0022	Missed study vaccination at Vaccination 3	Concomitant vaccine 2	Visit-level exclusions - Visit 5	30 Days Postdose 3
abc-0022	Missed study vaccination at Vaccination 3	Concomitant vaccine 3	Visit-level exclusions - Visit 5	30 Days Postdose 3
abc-0023	Missed at least one dose of CV1 at Vaccination 1, 2	Immunogenicity Category 1	Visit-level exclusions - Visit 3	30 Days Postdose 2
abc-0023	Missed at least one dose of CV1 at Vaccination 1, 2	Immunogenicity Category 2	Visit-level exclusions - Visit 3	30 Days Postdose 2
abc-0023	Missed at least one dose of CV1 at Vaccination 1, 2	Concomitant vaccine 1	Visit-level exclusions - Visit 3	30 Days Postdose 2
abc-0024	Missed Concomitant vaccine 2 at Vaccination 3	Immunogenicity Category 1	Visit-level exclusions - Visit 5	30 Days Postdose 3
abc-0024	Missed Concomitant vaccine 2 at Vaccination 3	Immunogenicity Category 2	Visit-level exclusions - Visit 5	30 Days Postdose 3
abc-0024	Missed Concomitant vaccine 2 at Vaccination 3	Concomitant vaccine 2	Visit-level exclusions - Visit 5	30 Days Postdose 3
abc-0025	Missed Concomitant vaccine 3 at Vaccination 3	Immunogenicity Category 1	Visit-level exclusions - Visit 5	30 Days Postdose 3
abc-0025	Missed Concomitant vaccine 3 at Vaccination 3	Immunogenicity Category 2	Visit-level exclusions - Visit 5	30 Days Postdose 3
abc-0025	Missed Concomitant vaccine 3 at Vaccination 3	Concomitant vaccine 3	Visit-level exclusions - Visit 5	30 Days Postdose 3

Table 8. Few rows from ADPDEV showing visit level exclusion due to missed dose(s)

4.3 SAS PROGRAMMING CHALLENGES AND SOLUTIONS

Now, let us look at some of the programming challenges that we encountered with solutions.

1. Received Incorrect treatment – This is a participant level exclusion for first dose and visit level exclusion for later doses after protocol violation. This exclusion can be challenging to implement as it involves determining which visits need to be excluded especially in scenarios where multiple study vaccines and multiple concomitant vaccines are present. A study design involving 3 doses and 3 concomitant vaccines is shown in Table 1. The specific immunogenicity results excluded depend on both the timing of the deviation and whether the deviation is related to study vaccine or concomitant vaccine as shown in Table 9. All the results after the deviation date are excluded. Below is a sample code and snapshot of dataset created to check if the deviation occurred before Visit 3 and not after Visit 4 or Visit 5 – see Table 10.

	Analyses for SV			Analyses for CV1	Analyses for CV2/CV3
Time of Deviation	**Visit 3 (30 Days PD2)**	**Visit 4[a] (Day 270)**	**Visit 5 (30 Days PD3)**	**Visit 3 (30 Days PD2)**	**Visit 5 (30 Days PD3)**
Deviations related to incorrect study medication					
At Visit 1	E	E	E	E	E
At Visit 2	E	E	E	E	E
At Visit 4	I	I	E	I	E
Deviations related to incorrect concomitant medication					
At Visit 1	E	E	E	I	I
At Visit 2	E	E	E	E	I
At Visit 4	I	I	E	I	E

[a] Serology samples for SV analyses were to be collected at Visit 4 prior to vaccination.
CV1=Concomitant Vaccine 1; CV2=Concomitant Vaccine 2; CV3=Concomitant Vaccine 3; E=Exclude; I=Include (do not exclude); PD=Postdose; SV=Study Vaccine.

Table 9. Exclusion criteria for receiving Incorrect treatment

In the below code, dv1 is the dataset that contains the Protocol deviation records of interest that is a subset of SDTM DV dataset merged with SDTM SV dataset to get the dates of visits 3, 4 and 5. The flag FL1 is set to “Y” for deviations occurring for Study vaccine and FL2 is set to “Y” for deviations occurring for concomitant vaccine 1. The flags FL1 and FL2 are intermediate variables and not part of the final ADPDEV dataset.

```
data row2;
  set dv1;
  if (( dvstdt < visit3 ) and missing(dvstdt) ne 1 and missing(visit3) ne 1) or
     (missing(visit3)=1 and not(dvstdt=visit4>. ) and not(dvstdt>=visit5>. )) then do;
     if FL1 = "Y" then do; /* If the deviation occurred for the Study vaccine */
       ACAT1='Immunogenicity Category 1';
       avisit='30 Days Postdose 2'; avisitn=3; acat2="Visit-level exclusions - Visit 3";acat2n=2;
       output;
       avisit='Prior to Dose 3'; avisitn=4; acat2="Visit-level exclusions - Visit 4"; acat2n=3;
       output;
       avisit='30 Days Postdose 3'; avisitn=5;acat2="Visit-level exclusions - Visit 5"; acat2n=4;
       output;
       ACAT1='Immunogenicity Category 2';
       avisit='30 Days Postdose 2'; avisitn=3; acat2="Visit-level exclusions - Visit 3";acat2n=2;
       output;
       avisit='Prior to Dose 3'; avisitn=4; acat2="Visit-level exclusions - Visit 4"; acat2n=3;
       output;
       avisit='30 Days Postdose 3'; avisitn=5;acat2="Visit-level exclusions - Visit 5"; acat2n=4;
       output;
       ACAT1='Concomitant vaccine 1';
       avisit='30 Days Postdose 2'; avisitn=3; acat2="Visit-level exclusions - Visit
       3";acat2n=2;output;
```

```
/* Code continued from previous page */

      avisit='30 Days Postdose 3'; avisitn=5;acat2="Visit-level exclusions - Visit
      5"; acat2n=4;
      ACAT1='Concomitant vaccine 2';output;
      ACAT1='Concomitant vaccine 3';output;
    end;
    if FL2 = "Y" then do; /* If the deviation occurred for the concomitant vaccine 1*/
      ACAT1='Immunogenicity Category 1';
      avisit='30 Days Postdose 2'; avisitn=3;acat2="Visit-level exclusions - Visit 3";acat2n=2;
      output;
      avisit='Prior to Dose 3';    avisitn=4;acat2="Visit-level exclusions - Visit 4"; acat2n=3;
      output;
      avisit='30 Days Postdose 3'; avisitn=5;acat2="Visit-level exclusions - Visit 5"; acat2n=4;
      output;
      ACAT1='Immunogenicity Category 2';
      avisit='30 Days Postdose 2'; avisitn=3;acat2="Visit-level exclusions - Visit 3";acat2n=2;
      output;
      avisit='Prior to Dose 3';    avisitn=4;acat2="Visit-level exclusions - Visit 4"; acat2n=3;
      output;
      avisit='30 Days Postdose 3'; avisitn=5;acat2="Visit-level exclusions - Visit 5"; acat2n=4;
      output;

      ACAT1='Concomitant vaccine 1';
      avisit='30 Days Postdose 2';avisitn=3;acat2="Visit-level exclusions - Visit 3";acat2n=2;
      output;
    end;
  end;
run;
```

USUBJID	ACAT1	ACAT2	FL1	AVISIT	FL2
abc-4567	Immunogenicity Category 1	Visit-level exclusions - Visit 3	Y	30 Days Postdose 2	
abc-4567	Immunogenicity Category 1	Visit-level exclusions - Visit 4	Y	Prior to Dose 3	
abc-4567	Immunogenicity Category 1	Visit-level exclusions - Visit 5	Y	30 Days Postdose 3	
abc-4567	Immunogenicity Category 2	Visit-level exclusions - Visit 3	Y	30 Days Postdose 2	
abc-4567	Immunogenicity Category 2	Visit-level exclusions - Visit 4	Y	Prior to Dose 3	
abc-4567	Immunogenicity Category 2	Visit-level exclusions - Visit 5	Y	30 Days Postdose 3	
abc-4567	Concomitant vaccine 1	Visit-level exclusions - Visit 4	Y	30 Days Postdose 2	
abc-4567	Concomitant vaccine 2	Visit-level exclusions - Visit 5	Y	30 Days Postdose 3	
abc-4567	Concomitant vaccine 3	Visit-level exclusions - Visit 5	Y	30 Days Postdose 3	
abc-6789	Immunogenicity Category 1	Visit-level exclusions - Visit 3		30 Days Postdose 2	Y
abc-6789	Immunogenicity Category 1	Visit-level exclusions - Visit 4		Prior to Dose 3	Y
abc-6789	Immunogenicity Category 1	Visit-level exclusions - Visit 5		30 Days Postdose 3	Y
abc-6789	Immunogenicity Category 2	Visit-level exclusions - Visit 3		30 Days Postdose 2	Y
abc-6789	Immunogenicity Category 2	Visit-level exclusions - Visit 4		Prior to Dose 3	Y
abc-6789	Immunogenicity Category 2	Visit-level exclusions - Visit 5		30 Days Postdose 3	Y
abc-6789	Concomitant vaccine 1	Visit-level exclusions - Visit 3		30 Days Postdose 2	Y

Table 10. Snapshot of important variables from ADPDEV for incorrect treatment received

2. Administered improperly stored study vaccine – If a participant was administered improperly stored study intervention that was deemed unacceptable for use, only immunogenicity results immediately following the occurrence of deviation date are excluded. Consider an example where Dose 3 has a deviation and only those administered at Visit 3 or Visit 5 are considered. In this case we check if the deviation occurred for the study vaccine, then only the Immunogenicity analyses related to study vaccine and the concomitant vaccines at that visit may be excluded.

   In the code provided below, dv1_2 represents the dataset containing the deviation data related to the improper storage of the administered study vaccine. The variable 'FL1' is a flag that determines whether the deviation occurred for the study vaccine. If this flag is triggered, it leads to the exclusion of analysis for Immunogenicity category 1, 2 and concomitant vaccine categories 2, 3 at '30 Days

Postdose 3'. On the other hand, the variable 'FL3' is a flag that determines if the deviation occurred for the second concomitant vaccine. When this flag is triggered, it results in the exclusion of analysis for Immunogenicity category 1, 2 and concomitant vaccine 2 at '30 Days Postdose 3' as shown in the snapshot (Table 11). The flags FL1 and FL3 are intermediate variables and not part of the final ADPDEV dataset.

```
data row3;
  set dv1_2;
  if missing(tr03sdt)=0 and (tr03sdt = dvstdt) then do;
    if FL1 = "Y" then do; /* If the deviation occurred for the Study vaccine */
      ACAT1='Immunogenicity Category 1';
      avisit='30 Days Postdose 3'; avisitn=5; acat2="Visit-level exclusions - Visit 5";
acat2n=4;
      output;
      ACAT1='Immunogenicity Category 2';
      avisit='30 Days Postdose 3'; avisitn=5; acat2="Visit-level exclusions - Visit 5";
acat2n=4;
      output;

      avisit='30 Days Postdose 3'; avisitn=5; acat2="Visit-level exclusions - Visit 5";
acat2n=4;
      ACAT1='Concomitant vaccine 2'; output;
      ACAT1='Concomitant vaccine 3'; output;
    end;
    if FL3 = "Y" then do; /* If the deviation occurred for the Concomitant vaccine 2 */
      ACAT1='Immunogenicity Category 1';
      avisit='30 Days Postdose 3'; avisitn=5; acat2="Visit-level exclusions - Visit 5";
acat2n=4;
      output;
      ACAT1='Immunogenicity Category 2';
      avisit='30 Days Postdose 3'; avisitn=5;acat2="Visit-level exclusions - Visit 5";
acat2n=4;
      output;

      ACAT1='Concomitant vaccine 2';
      avisit='30 Days Postdose 3'; avisitn=5;acat2="Visit-level exclusions - Visit 5";
acat2n=4;
      output;
    end;
  end;
run;
```

USUBJID	ACAT1	ACAT2	FL1	AVISIT	FL3
abc-3213	Immunogenicity Category 1	Visit-level exclusions - Visit 5	Y	30 Days Postdose 3	
abc-3213	Immunogenicity Category 2	Visit-level exclusions - Visit 5	Y	30 Days Postdose 3	
abc-3213	Concomitant vaccine 2	Visit-level exclusions - Visit 5	Y	30 Days Postdose 3	
abc-3213	Concomitant vaccine 3	Visit-level exclusions - Visit 5	Y	30 Days Postdose 3	
abc-3214	Immunogenicity Category 1	Visit-level exclusions - Visit 5		30 Days Postdose 3	Y
abc-3214	Immunogenicity Category 2	Visit-level exclusions - Visit 5		30 Days Postdose 3	Y
abc-3214	Concomitant vaccine 2	Visit-level exclusions - Visit 5		30 Days Postdose 3	Y

Table 11. Snapshot of important variables from ADPDEV for administration of improperly stored study vaccine

There might be more deviations than described above and the same approach can be followed to program the excluded visits. The final ADPDEV dataset is the union of all the records with excluded visits, deviation terms and corresponding analysis categories for each participant. This is used to derive the analysis flag in ADaM dataset for Immunogenicity.

5. CONCLUSION

This paper serves as a comprehensive guide for identifying and deriving records with protocol deviations in the ADPDEV dataset for vaccine studies. It provides a detailed explanation of the process, accompanied

by code examples and data snapshots, to facilitate the identification of participant and visit level exclusions. Furthermore, this paper addresses the challenges posed by studies involving multiple doses and multiple concomitant vaccinations, providing specific examples tailored to these complex scenarios. By showcasing how to handle protocol deviations in such studies, it offers valuable insights into common deviations that may occur. Importantly, the approach outlined in this paper has been successfully applied to generate the ADPDEV dataset for one of the vaccine studies, meeting all the necessary analysis requirements. This validates the effectiveness and practicality of the methodology presented.

Overall, this paper provides a comprehensive framework for programmatically identifying and dealing with protocol deviations in vaccine studies, enabling accurate and reliable analysis of the data.

6. REFERENCES

1. ADaM Structure for Occurrence Data (OCCDS) Implementation Guide 1.1 https://www.cdisc.org/standards/foundational/adam/adam-structure-occurrence-data-implementation-guide-v1-1

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8. CONTACT INFORMATION

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

Rashmi Gundaralahalli Ramesh
Merck & Co., Inc.
North Wales, PA, USA
rashmi.gundaralahalli@merck.com

Jeffrey Lavenberg
Merck & Co., Inc.
North Wales, PA, USA
jeffrey.lavenberg@merck.com