
Paper PO 53**Reporting of treatment emergent adverse events based on pooled data Analysis or Country Specific Submissions: A case study**

Sheetal Shiralkar- Independent Consultant. Plainsboro-NJ

Often sponsor need to file for regulatory submissions at different country specific regulatory authorities after they get approval from Food and Drug Administration. The key reporting aspect of country specific submissions pertaining to emerging markets involve accurate reporting of adverse events from the clinical trials conducted for the specific drug in those countries. For reporting of these adverse events, we need to develop a robust algorithm and comprehensive system architecture for efficient and accurate data representation.

Pooling of data from multiple studies is often the first step in ensuring that adverse events from all the trials of the drug get accurately reported. The data pooling specifications involve lot of conditioning and sub-setting of data based on reporting specifications. This poster describes a case study of a typical data pooling and reporting process of trial level data available in ADaM model. The analysis also elaborates on more details pertaining to reporting requirements and on programming algorithms developed to meet those requirements.

INTRODUCTION

Regulatory submission for new drug application (NDA) involves reporting of multiple trial level as well as pooled data analysis findings. This also involves pharmacovigilance which includes accurate reporting of adverse events. The patient recruitment for these trials happens across the world depending on how sponsor chooses and recruits the monitoring sites. Site selection process involves consideration of lot of factors including consideration of emerging markets as prospective sale of drug in those market after regulatory approval. As a part of pharmacovigilance, sponsors are required to do accurate reporting of adverse events for patients recruited from different countries at the regulatory authorities in those countries. This reporting involves series of data analysis and processing. As a first step the adverse events reporting data is created for one trial by merging the analysis datasets for exposure, demog, adverse events, and ADSL data. Then pooled data is created by merging such adverse events reporting datasets from multiple studies. Once pooled data is created, additional data processing algorithms are applied on this data depending on pharmacovigilance reporting needs. Such data is then used for country specific submissions by using its subset for country specific patient population. Data presentations (reports and graphs) are produced based on such data. In subsequent sections we will see this process in detail and will focus on typical algorithms applied on data processing requirements of such reporting.

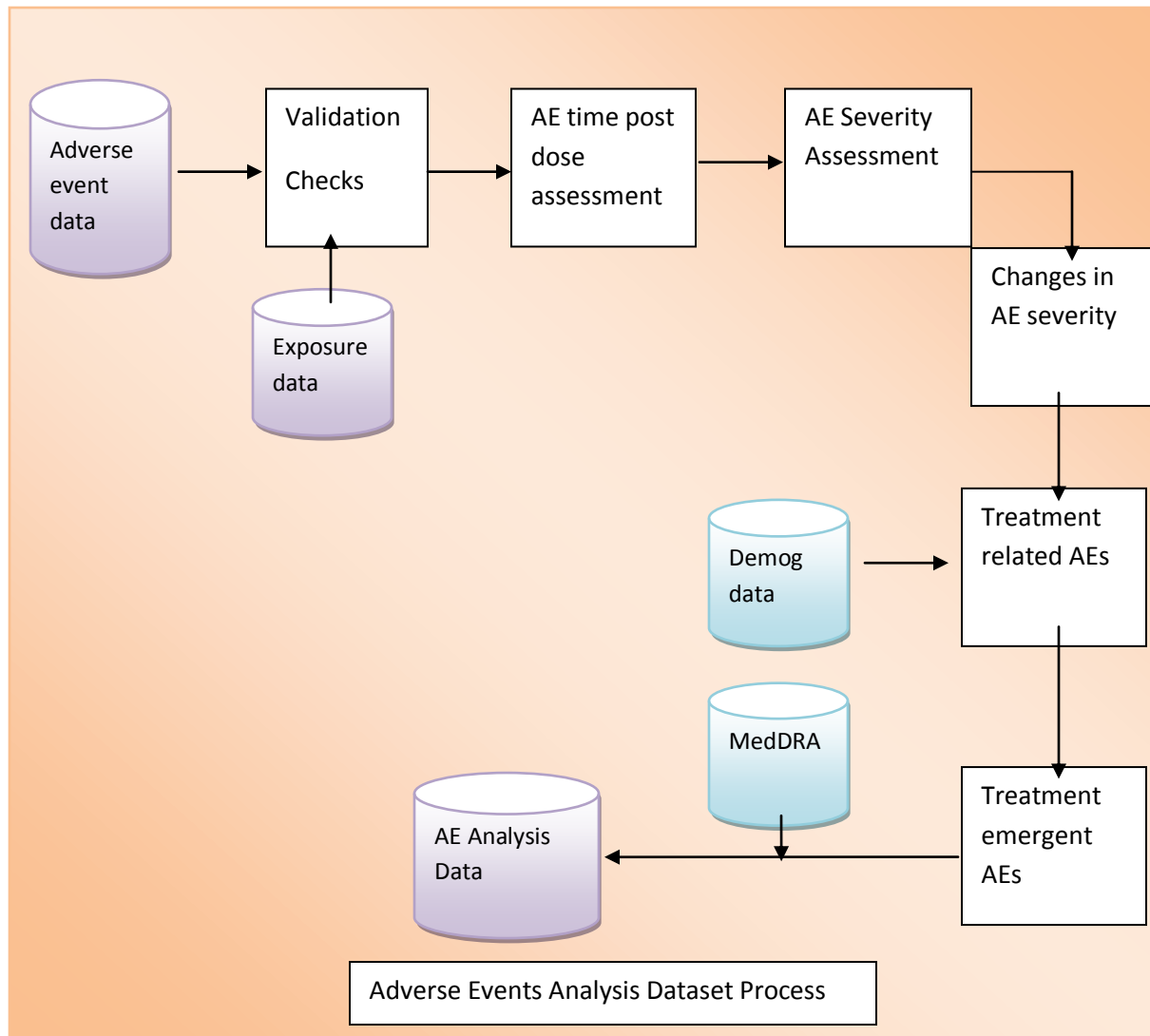
CREATING ADVERSE EVENT ANALYSIS DATA (ADAE):

As a first step in accurate adverse events reporting, it is important to apply correct algorithms on the adverse events data obtained from the database at trial level. In this section we will discuss the detailed algorithm of ADAE dataset. In this data processing we in-built some validation checks to ensure accurate implementation of programming algorithm. While using the adverse event data from the database, as a first step we ensure that the variables from the data follow necessary formats. This includes the following:

- 1) Ensuring that all 'required' and 'recommended' variables as per the SDTM requirements are present. Also, depending on analysis needs, it is important to ensure the presence and validity of permissible variables.
- 2) Ensuring that the data exists and the dataset is not blank.
- 3) Each variable should have appropriate length, format, label and informat as outlined in SDTM model.

Once above basic validation steps are done, adverse events occurrences are carefully synchronized against the drug exposure information from dosing data. The dates and time from both the datasets are carefully compared to determine relation of adverse events with drug exposure. In this process the adverse event time post dose is also calculated. Usually these data processing and merging with exposure data is done through a separate sub-set of macro. This mapping of adverse events time points against patient's treatment exposure is a very important step in adverse event reporting. This step needs thorough validation to ensure accuracy of analysis. After this process, the

adverse events are flagged on the basis of if they were present prior to start of drug treatment to patient or if they started after the drug treatment exposure.



Next important step in analysis involves determining severity of adverse events. This is assessed based on, if adverse event occurred during study treatment, i) was observed during an event that spans a period of study treatment, ii) was observed during the period prior to study treatment, or iii) if it was observed by cause. The severity assessment is one of the most important aspect of pharmacovigilance reporting and this assessment is used for multiple reporting needs down the road.

After severity assessment, the next step involves assessment of changes of severity of adverse events over the progression of trial. During treatment exposure the increases, decreases, or stability of severity of adverse events is assessed. The assessed severity is also compared against the treatment start and end data/time. Based on this assessment for reporting of this information, additional variables are derived in adverse events reporting data. These variables reflect if the adverse event severity was present before, started, or stopped during treatment. Usually with clinician's input emergence of adverse event is decided. In this step a flag is created to show if the adverse events are treatment emergent. Then additional variable is derived to show if the severity of adverse event was treatment emergent.

As a next step, patient demographic information such as gender, age, weight, race etc is added in adverse event reporting data by merging this analysis data with the demographic data from database. All new variable derived in the above processes are given appropriate formats, labels, lengths and other format related information.

Once this data is created, MedDRA dictionary information is added here. The version of dictionary to be utilized is decided by the sponsor. The adverse events are reported as they are experienced by the patients and as they are reported on case report form. These adverse event terms are considered as low level term. Then these are mapped against the corresponding low level terms in MedDRA and additional group level terms are populated from MedDRA to adverse event data. These include High Level Terms (HLTs), Preferred terms (PT), High level Group Terms (HLGTs) and system organ class specific information.

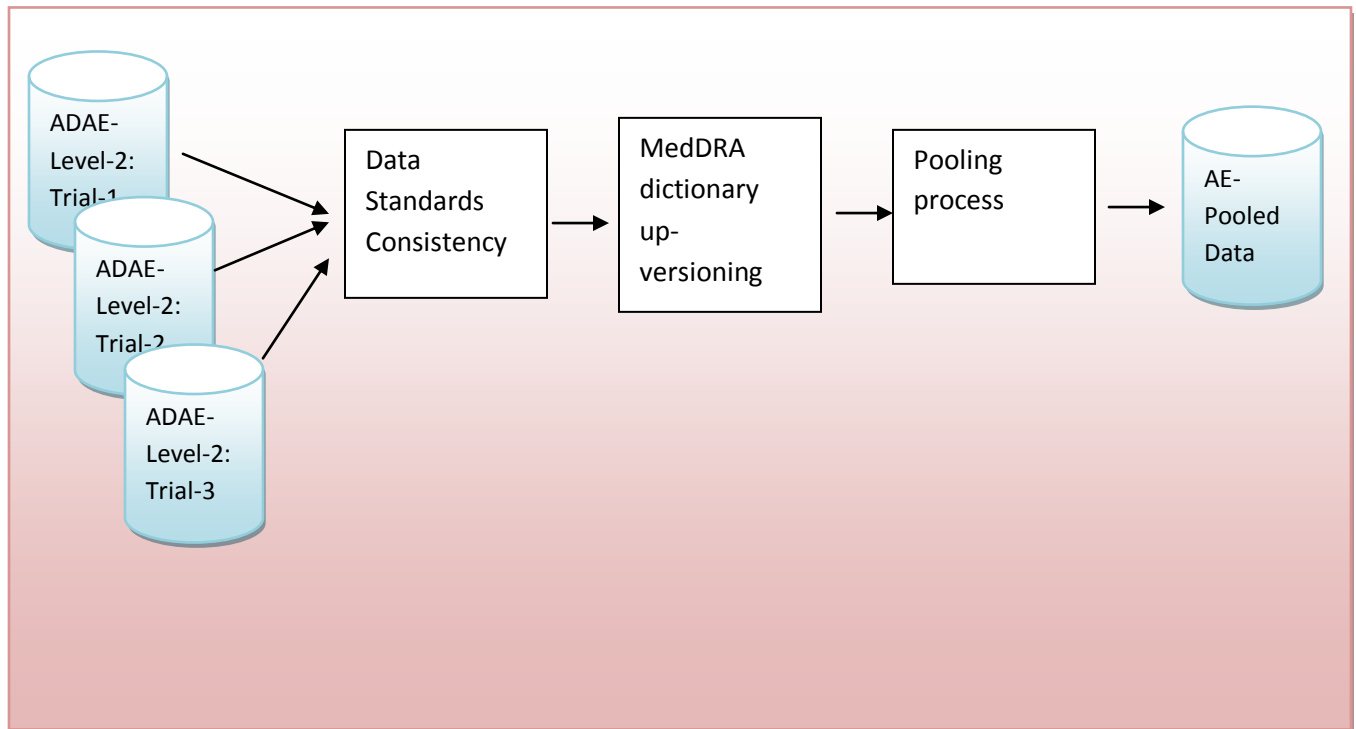
DEVELOPMENT OF AE REPORTING DATA:

As discussed in above section, we create ADAE by conducting series of algorithm processing to make sure that adverse event information is analyzed against the exposure data and we incorporate MedDRA dictionary information for consistent interpretation of adverse events reported. Although the ADAE is a complete data for adverse event reporting, when it comes to country specific submissions, it still lacks some information. In the ADSL (subject level analysis dataset), lot of useful information for analysis is present. This includes different flags pertaining to population sets such as safety population, per protocol population, and intent to treat population flags. In addition to this, the ADSL contains discontinuation specific information. For accurate reporting of AEs by these population sets, it is important that these key variables from ADSL are available for adverse event reporting.

Assessments of adverse events based on windowing or analysis based on the stages of trial in which these adverse events occur, is an important aspect of pharmacovigilance. In order to ensure that adverse event reporting accounts for these stages of trial, these events are counted against the flags from ADSL. This is achieved by merging the ADAE with ADSL and incorporating the flags and discontinuation specific information from ADSL to adverse event second level analysis dataset. At this point the adverse event reporting data is ready for the reporting for trial level adverse events.

Often the country specific submission involves multiple trials where the patient population from a specific country is enrolled and participated in clinical trials. Country specific submission involves reporting of adverse events for those particular trials as well as reporting for adverse events for pooled data. Above second level adverse event data which incorporates flags from ADSL meets the sufficiency purpose for reporting of adverse events at trial level. For pooled data reporting, such second level ADAE is pooled for multiple trials. The pooling of data involves ensuring careful interpretation of pooling specification to ensure selection of correct patient population. Secondly, considering different trial designs, the pooling involves appending the data from multiple trial in an appropriate manner so that the data can be grouped and analyzed without encountering errors. Such pooling becomes a bit tricky when one study is an extension of another study and a subset of patient population from one study is enrolled into second study. While conducting pooling of second level adverse event data from multiple studies it is important to pay attention to these critical factors. In many circumstances, depending on duration and time frame of trial conduct, sponsor may choose to use different versions of MedDRA dictionary. It is important that the pooled data uses one consistent version of MedDRA. This step may involve up-versioning of MedDRA for older trials before pooling the adverse event data from those trials.

Besides MedDRA up-versioning another aspect that plays a key role is the data standards used for different trials during the drug submission process. As an example, as a part of standards development process, during drug development process, some trials may have used SDTM-3.1.1 and others may have used SDTM-3.1.2. It is important that pooled data uses one homogenous standard for reporting. Following diagram depicts the pooling process:



Treatment emergent Adverse event is a very important component of safety analysis. There are so many standard reports which describe the severity and relationship to study drug. This reporting is based on MedDRA (Medical Dictionary for Regulatory Activities). MedDRA has multi-level of hierarchy, System Organ Class (SOC), High-Level Group Terms (HLGT), High-Level Terms (HLT), Preferred Terms (PT) and Lower-Level terms. The report generation algorithm involves following steps:

- 1) Reading the patients who completed the trial. Discontinued or withdrawn patients are assessed separately for adverse events. Adverse event reporting for active patients is considered as a part of country specific regulatory submission.
- 2) Read country specific population and subset data from ADSL, while sub-setting we will remove observation which are irrelevant and or are duplicate and keep specific variables pertaining to country and patient identification.
- 3) For calculating subject evaluable for adverse events reporting, we will merge exposure data and ADSL and subset for country specific population. Use procedure like proc freq or proc tabulate we will get the number of subject evaluable for Adverse event.

/* Below is the sample code to get no of subject evaluable for the AE */

```
PROC TABULATE DATA=adae2 order=data;

class extrt
```

```
table extrt=' ' *n='';
run;
```

- 4) Now we read Adverse event data , subset data for treatment emergent adverse event . Adverse event data merged with country specific population data from ADSL. After merging we will get the adverse event data used for report generation. After putting appropriate sorting procedure, we use following sample code to merge datasets.

```
/* Merging Datasets */
DATA aefinal;
merge ae (in=a) country (in=b);
by studyid;
if a;
run;
DATA aefinal;
set aefinal;
where upcase(country) in ('CHINA');
run;
```

- 5) After getting Adverse event final data , in following data step we select treatment emergent flag with the sub-setting or unidirectional 'if statement'. We choose first observation to ensure we capture AE start information and create one variable 'emerge' for getting incremental reports for treatment emergent events.

```
PROC SORT DATA=aefinal;
by pid sort extrt aeterm aestdtc emerge;
run;
DATA aefinal;
set aefinal;
by pid sort aetext;
if emerge=1 and first.aeterm then do; femerge=1; end; run;
run;
```

- 6) Following code segment shows derivation for getting monthly interval , (0to 6) (6 to 12) , (12 to 18)and (18 to 24). For getting monthly interval we are creating one new variable 'aeday' . We get this information from

analysis plan or statistical analysis plan drafted by statisticians. This variable creates with the condition which is as follow,

```
DATA aefinal;

    set aefinal;

    if aestdtc ne . then do;

        aeday= aestdtc-exstdtc +1;

        If 1 <= aeday <=180 then m6=1;

/* Else if 181 <= aeday <=360 then m6to12=1;

        Else if 361 <= aeday <=540 then m12to18=1;

        Else if 541 <= aeday <=720 then m18to24=1;

        Else if aeday >720 then m24=1;

    */

end;

run;
```

- 7) After the above derivations adverse event final data is ready to get Incremental reports. At this point we need to specify sorting, implementation, and selection of appropriate variables depending on reporting needs. By using the “Where” statement, we select time interval, treatment emergent adverse event, country specific population as well as active patient population from the data. In some reports we need to select specific protocols too. After this step we get targeted adverse event dataset on which we can apply reporting procedures like proc report or proc tabulate. SQL procedure is used to get the no of subject discontinue due to adverse event.
- 8) Final step of Treatment emergent adverse event report generation is, computation and tabulation of number of patients with Adverse event disorder. For getting counts of each category, data sorting is very important. So first we need to sort data with bodytext, higher group level terms and preferred terms. Sample code illustrating use of SQL to get such counts for reports is as follows:

```
proc sql;

/** counts in each SOC ***/

create table soccnt as

select extrt, bodytext, count(distinct(subjid)) as soccnt

from aefinalf

group by extrt, bodytext

;

/** counts by SOC, HLGTEXT ***/
```

```

create table sochlgcnt as

select extrt, bodytext, hlgtext, count(distinct(subjid)) as sochlgcnt

from aefinalf

group by extrt, bodytext, hlgtext

;

/** counts by SOC, HLGTEXT, PREFTEXT ****/

create table shprt_cnt as

select extrt, bodytext, hlgtext, preftext, count(distinct(subjid)) as prtextcnt

from aefinalf

group by extrt, bodytext, hlgtext, preftext

;

quit;

```

Some of the typical adverse event reports that are produced for country specific submissions by using above algorithmic steps are as follows. These examples show incremental reports.

Table	xxx.x.x.	Treatment-Emergent Adverse Events by System Organ Class (All Causalities) – Country XXX Patients
Table	xxx.x.x.	Treatment-Emergent Adverse Events by SOC, HLG and PT (All Causalities) – Country XXX patients , Months 0-6
Table	xxx.x.x	Treatment-Emergent Adverse Events by SOC, HLG and PT (All Causalities) – Country XXX patients, Months 6-12
Table	xxx.x.x.	Treatment-Emergent Adverse Events by SOC, HLG and PT (All Causalities) – Country XXX patients, Months 12-18
Table	xxx.xx.x	Exposure Estimates and Incidence Rates for Discontinuations due to Adverse (All Causalities)- All Patients
Table	xxx.xx.x	Exposure Estimates and Incidence Rates for All Serious Adverse Event (All Causalities)- All Patients

CONCLUSION

Sponsors often choose to country specific submissions as a part of their wider strategy to sell the new drug in emerging markets. In order to execute this strategy, sponsor often needs to expedite the regulatory submissions to different regulatory authorities across the globe. Adverse events reporting is a part of larger pharmacovigilance reporting needs for any new drug that has been approved by Food and Drug Administration (FDA). As discussed in this paper, the adverse event reporting involves lot of steps with systematically planned and executed algorithms. For accurate reporting of adverse events by considering various regulatory reporting needs, it is important to carefully execute the planned algorithm development. This paper does not discuss the larger aspect of serious adverse events

reporting or reporting of adverse events when the patients are not active in trial conduct phase. As a part of larger pharmacovigilance strategy complete reporting of adverse events is conducted.

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REFERENCES

- 1) Clinical Data Interchange Standards Consortium, ADaM and SDTM models. All CDISC standard guidelines and documentation can be found at: <http://www.cdisc.org>
- 2) Medical dictionary, MedDRA Terminology is available at <http://www.meddrasso.com>

CONTACT INFORMATION: Your comment and question are valued and encouraged. Author can be contacted at sheetalshiralkar@gmail.com

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