Introduction to Annual Reporting for Beginners!

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ABSTRACT

In clinical trials, the safety information of the investigational drug plays a critical role. Regular analysis of safety is crucial for the assessment of risk to trial participants and to understand the risk vs. benefit of the medicinal product. Summaries of safety information are submitted to the regulators and other committees at regular periodic intervals to monitor the safety profile of an investigational drug.

The Development Safety Update Report (DSUR) is the pre-marketing equivalent of the post-marketing Periodic Benefit-Risk Evaluation Report (PBRER). The DSUR goal aims to assess risk and any changes in risk since the previous DSUR, while the PBRER goal is to present a comprehensive and critical analysis of new or emerging information on the risks of the drug.

Both the DSUR and PBRER are produced once every six months, annually or less frequently, based on national or regulatory requirements. These reports evaluate adverse events that occur during the clinical trial as tracking them is vital in determining if the event is related to the investigational drug. Also, the demographics of the participants, whether participants complete or discontinue the study, why they discontinue the study, and information related to death and exposure are captured in the tables and listings.

This paper focuses on the approach of handling multiple studies across an indication and the detailed information of the outputs that are required for submission. It introduces a flexible reporting system with examples and programming solutions to generate the reports required for the regulatory submission.

INTRODUCTION

During the clinical development of any investigational drug, the safety information is submitted to regulatory authorities periodically. The periodic reports are of various forms such as DSUR, PBRER, and IB (Investigational Brochure) which have different requirements.

According to FDA's Guidance for Industry – Development Safety Update Report (based on ICH E2F), a DSUR is intended to be a common standard for periodic reporting on drugs under development (including marketed drugs that are under further study) among the ICH regions. US and EU regulators consider that the DSUR, submitted annually, would meet national and regional requirements currently met by the US IND Annual Report and the EU Annual Safety Report, respectively, and can therefore take the place of these existing reports. The main objective of a DSUR is to present a comprehensive, thoughtful annual review and evaluation of pertinent safety information collected during the reporting period related to a drug under investigation.

According to FDA's Guidance for Industry – Periodic Benefit-Risk Evaluation Report (based on ICH E2C(R2)) for PBRER, the guidance describes a common standard for periodic benefit-risk evaluation reporting on marketed products (including approved drugs that are under further study) among the ICH regions. The main objective of a PBRER is to present a comprehensive, concise, and critical analysis of new or emerging information on the risks of the medicinal product, and on its benefit in approved indications, to enable an appraisal of the product's overall benefit-risk profile.

The purpose of this paper is to describe the reports that are generated by the statistical programmers to support the preparation of DSUR and PBRER. The focus of the paper is to benefit the programmers who are involved in generating the data sets, tables, and listings and the clinical drug safety group who co-ordinate with the statisticians and programmers for producing high quality outputs.

WORKFLOW FOR THE DEVELOPMENT OF REPORTS

This section describes the typical and preferred workflow for the development of outputs from the time of request to delivery. Components may differ between companies:

- The Product Lead Scientist from clinical pharmacology group notifies the product lead Biostatistician (or designee) of the reporting period and the list of studies to be included in the DSUR or PBRER well in advance of the reporting period end date, such as 2 months prior or few weeks before the reporting period end date
- The Product Lead Biostatistician communicates with the Study Lead Programmer (SLP) about the product specifications to convey study information they need to fulfill the request.
- The SLP interacts with Clinical Data Management (CDM) about the data snapshot request. On the day of the snapshot date, CDM refreshes the data and notifies SLP that the data is ready.
- The study programming (SP) team follows the following steps for generating the outputs:
  - A few weeks prior to the data snapshot date (per timelines), generates a dry run with draft output for the Biostatistician to review
  - After the Biostatistician provides feedback, the SP team incorporates the comments and generates additional dry runs, as needed, until the output is ready for final production
  - On the data snapshot date, when CDM confirms the data is ready, the SLP or CDM creates a data snapshot and saves the data in the respective project folder/directory
  - Within a given timeframe (as agreed in the timelines) after the data snapshot date, the SP team produces the final version of the outputs in RTF or PDF format and requests Biostatistician review
- The Biostatistician (or designee) reviews the final outputs and informs the regulatory group that the DSUR and PBRER outputs are ready
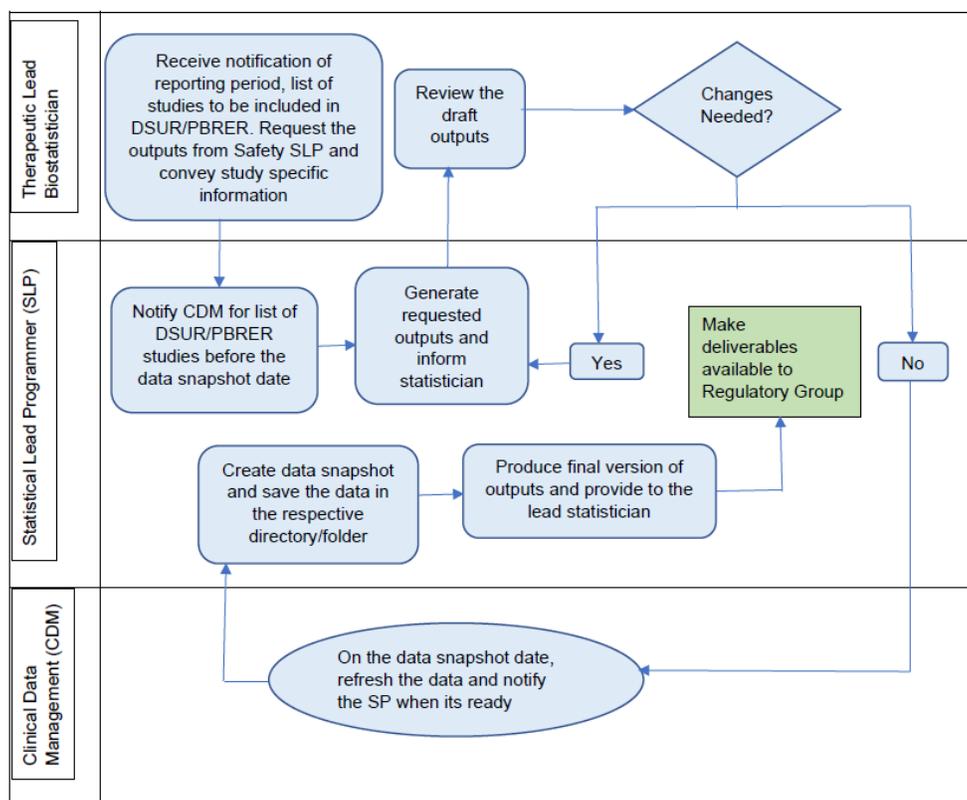

Figure 1: Workflow for development of the reports

FREQUENTLY ASKED QUESTIONS FOR GENERATING THE OUTPUTS

WHICH STUDIES TO INCLUDE?

DSURs and PBRERs provide all the safety information from all ongoing studies, and other studies that the sponsor is conducting or has completed during the review period. An ongoing clinical study for the purpose of a DSUR or PBRER is defined as a study where enrollment has begun, whether or not a hold is in place or analysis is complete, but without a clinical study report being available. A completed clinical study for the purposes of a DSUR or PBRER is defined as a study for which a clinical study report is available.

WHICH SUBJECTS TO INCLUDE?

Blinded and Unblinded studies: Randomized participants
Open-label Studies: Participants that have received the Investigational Drug

WHAT IS THE REPORTING PERIOD?

The Development International Birth Date (DIBD) is used to determine the start of the reporting period and is used as sponsor's first authorization to conduct a clinical trial. The date (year month and day) designated as the cut-off for snapshot data is considered the Data lock Point. This is used to determine the last day of the annual reporting period for DSUR and PBRER. SP receives the start and end date of the reporting period from the clinical safety group.

WHAT DATA SOURCE TO USE?

Ongoing Studies: Raw/CRF data or Study Data Tabulation Model (SDTM) data sets are used.
Completed Studies: Analysis Data Model (ADaM) are used.

ARE THERE ANY SPECIFIC DERIVATIONS/SELECTION CRITERIA?

- Exposure column should contain all exposed subjects since the start of the study, and the algorithm for deriving treatment duration usually follows the same logic as used in their respective study
- Calculation of age also remains the same as per respective study derivation
- Duration of treatment is displayed in days
- Scope of Adverse Event Inclusion: Any adverse event that starts or ends between the subject's first treatment and the end of any washout period

OTHER QUESTIONS?

Other commonly asked questions include:
- Titles and footnotes in the outputs
- Columns, derivation, and specification for the values in those columns to be displayed in the output

INPUT DATA SOURCE FOR GENERATING THE OUTPUTS

This paper focuses on the approach of using an integrated safety database to generate the DSUR and PBRER reports.

The integration process involves understanding the study design, selecting data sources, comparing, and analyzing the data and resolving the challenges faced while integrating multiple studies such as identifying the critical variables required for the analysis, evolving MedDRA dictionary versions, standardizing the pooled variable attributes such as variable length, type, label, and formats.

To generate the integrated pooled data sets, the following three steps are followed:

1. Identify the list of studies and tabulate the study-related information in an Excel file.
2. Create data set specifications with the list of derivations for generating analysis data sets.
3. Produce pooled analysis data sets.

1. IDENTIFY LIST OF STUDIES INFORMATION AND TABULATE IN EXCEL FILE

To illustrate the outputs in the following sections, a mocked-up integrated analysis data set specification will be used. To represent the concept of handling multiple studies, a simple scenario is considered as shown in Figure 2, where the indication of the project is "Oncology (ON)" and the therapeutic area is "123" which includes five studies: 01, 02, 03, 04, and 05.

Study Number	Blinded Study?	Unblinded Study?	Number of Arms	Investigational Drug Name	Data Source	Representation of the Data in the Output
ON123-01	yes		1	Drug A	Raw	Only Total Column is displayed
ON123-02	yes		1	Drug A	Raw	Only Total Column is displayed
ON123-03		yes	2	Drug A, Drug B	SDTM	Both the colums plus total column will be displayed
ON123-04		yes	2	Drug A, Drug A+ Drug B	SDTM	Both the colums plus total column will be displayed
ON123-05		yes	2	Drug A, Drug C	ADaM	Both the colums plus total column will be displayed

Figure 2: Mocked-Up Representation of the study related information

Note in Figure 2, the list of studies which will be used for DSUR and PBRER are outlined.

2. CREATE DATA SET SPECIFICATION WITH LIST OF DERIVATIONS FOR GENERATING ANALYSIS DATA SETS

In Figure 3, the critical variables that are required for generating the outputs are identified based on the mock shells of the outputs. These mock shells are usually provided by the lead therapeutic biostatistician. The "Names" and "Labels" columns represent the pooled analysis variable name and label, respectively. The other three columns represent derivations for different sources of data such as Raw/CRF data sets, SDTM data sets, and ADaM data sets. So, we can use different sources of data for creating the pooled data sets for generating the DSUR and PBRER reports.

Names	Labels	Derivations for raw (RAVE database) datasets	Derivations for SDTM data sets	Derivations for ADaM datasets
AETERM	Reported term	AE.AETERM	AE.AETERM	ADAE.AETERM
AEDECOD	Preferred term	AE.AEDECOD	AE.AEDECOD	ADAE.AEDECOD
AEBODSYS	System organ class	AE.AEBODSYS	AE.AEBODSYS	ADAE.AEBODSYS
AESER	AE serious flag	AE.AESER	AE.AESER	ADAE.AESER
AESTDTC	AE onset date character	Convert AE.AESTDAT_RAW and AE.AESTTIM to datetime format	AE.AESTDTC	ADAE.AESTDTC
AEENDTC	AE resolution date character	AE.AEENDAT_RAW and AE.AEENTIM to datetime format	AE.AENDTC	ADAE.AENDTC
ASTDT	Analysis AE onset date	Datepart of AESTDTC	Datepart o AESTDTC	ADAE.ASTDT
AENDT	Analysis AE resolution date	Datepart of AEENDTC	Datepart of AEENDTC	ADAE.AENDT
ASTDTM	Analysis AE onset datetime	Numeric datetime form of AESTDTC if its a full valid date	Numeric datetime form of AESTDTC if its a full valid date	ADAE.ASTDTM
AENDTM	Analysis AE resolution datetime	Numeric datetime form of AEENDTC if its a full valid date	Numeric datetime form of AEENDTC if its a full valid date	ADAE.AENDTM
AEREL	AE related flag	AE.AEREL	AE.AEREL	ADAE.AREL
AETOXGR	AE CTC grade	AE.AETOXGR	AE.AETOXGR	ADAE.ATOXGR
AECONTRT	AE treatment given	AE.ACNMED	SUPPAE.ACNMED	ADAE.ACNMED
AEACN	AE action taken	AE.AEACN	AE.AEACN	ADAE.AEACN
AEDISCFL	AE leading to discontinuation flag	Set to "Y" if any of following conditions met AEACN="DRUG WITHDRAWN"; AE.AEDIS='Yes';	Set to "Y" if any of following conditions met AEACN="DRUG WITHDRAWN"; SUPPAE.AEDIS='Y';	ADAE.AEDISCFL
AESDTH	AE death flag	Set to 'Y' when AE.AESDTH='Yes';	Set AE.AESDTH	ADAE.AESDTH
AEVER	MedDRA version	AE.AEVER	SUPPAE.AEVER	ADAE.AEVER
AEONGFL	AE ongoing flag	Set to Y if AEONGO=1;	Set to Y if AEENRF='ONGOING'	Set to Y if AEENRF='ONGOING'

Figure 3: Mocked-Up Specification Document of "Pooled Adverse Events" Data Set

Similarly, [Figure 4](#), presents the variables for a pooled ADSL-like subject-level data set

Names	Labels	Derivations for raw (RAVE database) data sets	Derivations for SDTM data sets	Derivations for ADaM data sets
STUDYID	Study ID	DEMOG.PROJECT	Set to DM.STUDYID	Set to ADSL.STUDYID
USUBJID	Unique subject ID	Concatenation of PROJECT, SITE, SUBJECT separated by '-'	Set to DM.USUBJID	Set to ADSL.USUBJID
SITEID	Site ID	DEMOG.SITE	Set to DM.SITEID	Set to ADSL.SITEID
SUBJID	Subject ID	DEMOG.SUBJECT	Set to DM.SUBJID	Set to ADSL.SUBJID
RFICDT	Date of informed consent	Numeric date form of CONSENT.IEDTC	Set to datepart of DS.DSSTDTC where DS.DECOD="Informed Consent Obtained"	Set to ADSL.RFICDT
RANDDT	Randomization date	Numeric date form of RANDOM.RANDTC	Set to datepart of DS.DSSTDTC where DS.DSDECOD="RANDOMIZED"	Set to ADSL.RANDDT
TRTSDT	First dosing date	Take the date part of earliest nonmissing EX.EXSTDTC where EXDOSE is non missing. Exclude dates after cutoff date from analysis	Take the date part of earliest nonmissing EX.EXSTDTC where EXDOSE is non missing. Exclude dates after cutoff date from analysis.	Set to ADSL.TRTSDT
TRTEDT	Last dosing date	Take the date part of latest nonmissing EX.EXSTDTC and EXENDTC where EXDOSE is non missing. Exclude dates after cutoff date from analysis	Take the date part of latest nonmissing EX.EXSTDTC and EXENDTC where EXDOSE is non missing. Exclude dates after cutoff date from analysis.	Set to ADSL.TRTEDT
ENRLFL	Enrolled population flag	Set to "Y" if CONSENT.IEDTC is not missing and CONSENT.IEDTC is less than or equal to data reporting end date	Set to "Y" if RFICDT is not missing and RFICDT is less than or equal to data reporting end date	Set to ADSL.ENRLFL
RANDFL	Randomized population flag	Set to "Y" if atleast one of the following holds for enrolled subjects: 1) non missing RANDDT and RANDDT is less than or equal to cutoff date	Set to "Y" where DS.DSDECOD='RANDOMIZED'	Set to ADSL.RANDFL
SAFFL	Treated population flag	Set to "Y" for enrolled subjects if TRTSDT is not missing. Else set to "N"	Set to "Y" for enrolled subjects if TRTSDT is not missing. Else set to "N"	Set to ADSL.SAFFL
AGEU	Age units	Set to 'Years'	Set to DM.AGEU	Set to ADSL.AGEU
AGE	Age at consent	DEMOG.AGE	Set to DM.AGE	Set to ADSL.AGE
AGECAT	Age categorization	Derive as per study categorization. For instance, "Set to "<65" if age is less than 65. else set to ">=65" if age is greater than or equal to 65	Derive as per study categorization. For instance, "Set to "<65" if age is less than 65. else set to ">=65" if age is greater than or equal to 65	Set to ADSL.AGECAT
ACTARM	Actual treatment	Set to IVRS.ARMNAME	Set to DM.ACTARM	Set to ADSL.ACTARM
ARM	Planned treatment	Set to IVRS.ARM	Set to DM.ARM	Set to ADSL.ARM
SEX	Sex	DEMOG.SEX	Set to DM.SEX	Set to ADSL.SEX
RACE	Race	DEMOG.RACE	Set to DM.RACE	Set to ADSL.RACE
DTHDT	Analysis death date	Numeric date form of DEATH.DDDAT_RAW	Numeric form of DM.DTHDTC	Set to ADSL.DTHDT
DTHDTC	Death date character	DEATH.DDDAT_RAW	Set to DM.DTHDTC	Character date form of ADSL.DTHDT
DTHREAS	Cause of death	DEATH.DDREAS	DS.DSTERM where DS.DSDECOD= "DEATH"	Set to ADSL.DTHREAS
DTHFL	Death flag	Set to "Y" if one of the following conditions are met: DTHDTC is not blank; DTHREAS is not blank; AE.AETOXGR='Grade 5'; AE.AEOUT='Fatal'; AE.AESDTH='Yes'	Set to DM.DTHFL	Set to ADSL.DTHFL
TRTDURD	Treatment duration in days	Set to (TRTEDT-TRTSDT)+1	Set to (TRTEDT-TRTSDT)+1	Set to (TRTEDT-TRTSDT)+1

Figure 4: Mocked-Up Specification Document of "Pooled Subject information" Data Set

3. PRODUCE POOLED ANALYSIS DATA SETS

Statistical Programmers use SAS® programming to develop the pooled integrated data sets. Using the data set specification document, the following two data sets are produced:

- Pooled Subject Information Data set
- Pooled Adverse Events Data set

REPORTS GENERATED BY STATISTICAL PROGRAMMERS

By using various SAS® procedures such as PROC FREQ, PROC MEANS, PROC REPORT, PROC UNIVARIATE, etc., and referring to pooled analysis data sets and mock shells, the statistical programmer will generate the following standardized output files for DSUR and PBRER submissions:

- Table 1: Cumulative Subject Exposure to Investigational Drug from Completed Clinical Trials, by Age and Sex

- Table 2: Cumulative Subject Exposure to Investigational Drug from Completed Clinical Trials, by Racial Group

- Table 3: Cumulative Summary Tabulations of Serious Adverse Events

- Table 4: Estimated Cumulative Subject Exposure

- Listing 1: Listing of Subjects who Died During the Reporting period in Clinical Trials

- Listing 2: Listing of Subjects who Discontinued Treatment Due to Adverse Events in Clinical Trials

As mentioned earlier, mock shells are needed to generate cumulative subject exposure tables and safety listings along with pooled analysis data sets. Below are the sample mock shells provided for completed clinical trials. Even for ongoing trials, the statistician will provide similar types of mock shells.

‹Drug›
Cumulative Subject Exposure to Investigational Drug from Completed Clinical Trials by Age and Sex

Age Range	Male	Female	Total
18 - 64	x	x	x
>=65	x	x	x
Missing	x	x	x
Total	x	x	x

* Data from completed trials as of [date]

Figure 5: Cumulative Subject Exposure to Investigational Drug from Completed Clinical Trials, by Age and Sex

‹Drug›
Cumulative Subject Exposure to Investigational Drug from Completed Clinical Trials by Racial Group

Racial Group	Number of Subjects
Asian	x
Black	x
Caucasian	x
White	x
Other	x
Unknown	x
Missing	x
Total	x

* Data from completed studies as of [date]

Figure 6: Cumulative Subject Exposure to Investigational Drug from Completed Clinical Trials by Racial Group

To summarize the Figure 5 mock shell, the number of male, female and total subjects with different age ranges are displayed in the final output. Figure 6 output represents number of subjects in each race category. To generate Figure 5 and Figure 6 outputs, the pooled subject information analysis data set is used as source data set and generate counts using PROC FREQ and produce output in RTF or PDF

format. The subset should include all subjects enrolled or randomized in the study who received any study treatment.

\<Drug\>

Cumulative Summary Tabulation of Serious Adverse Events (SAEs)

System Organ Class Preferred Term	Drug	Comparator
Investigations	x	x
Alanine aminotransferase increased	x	x
Aspartate aminotransferase increased	x	x
Nervous System disorders	x	x
Syncope	x	x

Figure 7: Cumulative Summary Tabulation of Serious Adverse Events (SAEs)

The above Figure 7 should specify the cumulative summary of Serious Adverse Events by System Organ Class, Preferred Term for Investigational Drug as well as for the Comparator Arm. The pooled adverse events data set is used as source data, and it has all the required variables to generate the output.

\<Drug\>

Estimated Cumulative Subject Exposure

Study Name	Enrolled	Drug	Comparator
ON123-01	x	x	x
ON123-02	x	x	x
ON123-03	x	x	x
ON123-04	x	x	x
ON123-05	x	x	x

Figure 8: Estimated Cumulative Subject Exposure

The above Figure 8 represents the estimates of cumulative subject exposure, based upon actual exposure data from completed clinical trials and the enrollment or randomization schemes for ongoing trials. This report has all the information of cumulative number of subjects enrolled, the number exposed to the investigational drug, as well as comparator arm for each study from ongoing and completed clinical trials.

\<Drug\>

Listing of Subjects Who Died During the Reporting Period in Clinical Trials

Study Name	Subject	Treatment Arm	First dose Date	Death Date	Cause of Death
ON123-01	001	x	x	x	x
ON123-02	003	x	x	x	x
ON123-03	010	x	x	x	x
ON123-04	016	x	x	x	x
ON123-05	021	x	x	x	x

Figure 9: Listing of Subjects Who Died During the Reporting Period in Clinical Trials

<Drug>

Listing of Subjects Who Discontinued Treatment Due to Adverse Events in Clinical Trials

Study Name	Subject	Treatment Arm	First Dose Date	Adverse Event
ON123-01	001	x	x	x
ON123-02	003	x	x	x
ON123-03	010	x	x	x
ON123-04	016	x	x	x
ON123-05	021	x	x	x

Figure 10: Listing of Subjects Who Discontinued Treatment Due to Adverse Events in Clinical Trials

The pooled subject information and adverse event data sets are used to generate the listings shown in Figure 9 and Figure 10, respectively. These lists out all the subject's information such as subject number, treatment arm, date subject received the treatment, date of death, reason for the death, and the adverse event that is reported for the treatment discontinuation, for every study in chronological order.

CONCLUSION

This paper introduced the concept of DSUR and PBRER to statistical programmers who have not worked on them earlier. The paper provides a simple and easy approach and an overall idea of the critical variables that are required for analysis and the tables and listings produced for the periodic submission.

REFERENCES

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