A utility to combine study level outputs to one PDF file for development safety update report (DSUR) regional appendices

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ABSTRACT

During clinical development, periodic analysis of safety information is crucial for the assessment of potential risks to trial participants. This information is important for health authorities (HAs) to evaluate the safety profile of the investigational drug on a regular basis. As one of the safety aggregate reports, the Development Safety Update Report (DSUR) provides a periodic update on drug safety information. The statistical programming team plays an important role in the DSUR process as they are responsible for generating both cumulative and reporting period outputs to support DSUR. This paper addresses the generation of two regional listings which are provided to DSUR region specific. Additionally, the paper introduces a SAS® macro that generates consolidated PDF files from sets of individual study SAS listings. The resulting PDF file(s) contains all the converted listings with self-extracted and properly sorted bookmarks. The macro package is a valuable tool that converts and combines individual study listings in .lst format into one or more submission ready compliant (SRC) PDF files for DSUR submission.

INTRODUCTION

During the clinical development of any investigational drug, safety aggregate reports (SARs) are submitted to health authorities periodically. The SARs include but are not limited to Drug Safety Update Report (DSUR), Periodic Benefit Risk Evaluation Report (PBRER), Investigational New Drug (IND) Safety Report, and Investigator's Brochure (IB) Annual Report. Each report has different requirements. Based on E2F Development Safety Update Report (fda.gov), the main objective of a DSUR is to present a comprehensive, thorough annual review and evaluation of pertinent safety information collected during the reporting period related to the drug under investigation. Pharmaceutical companies provide periodic DSUR to meet regulatory requirements. DSUR summarizes safety data arising from the worldwide clinical development program received by the company during the reporting period. From E2F section 16, we can see two reporting period outputs are required for DSUR in addition to cumulative outputs: they are "List of subjects who died during the reporting period" and "List of subjects who dropped out of clinical trials in association with an adverse event during the reporting period".

The objective of this paper is to outline the procedure for producing outputs for the DSUR, with a specific emphasis on two regional listings for subjects who died during the reporting period and subjects who dropped out of the studies due to adverse events. In accordance with regulatory guidelines, the two listings should provide key information on all SARs reported from the sponsor's clinical studies during the reporting period. The data should be organized by study for easy reference. In our company, the study level listings are created and then sent to study team (i.e. study statistician) for review. Subsequently, the individual study outputs are combined into PDF files for two regional listings: R2 list of subjects who died during the reporting period and R3 list of subjects who dropped out of studies during the reporting period. To speed up the regulatory submission, we have developed a SAS macro that converts and combines SAS outputs with the file extension .lst into a single consolidated PDF file. This paper presents the implementation details of this SAS macro and show how it can be used to streamline the generation of PDF file to support regulatory submission.

PROCESS FLOW FOR GENERATING DSUR OUTPUTS

This section describes the process flow for DSUR outputs (Figure 1). After receiving the list of studies and the data lock point (DLP) date, the project team prepares DSUR table shells and pooled datasets specification. It can be challenging to produce the pooled analysis datasets for a big asset with many protocols because the data format for each study may be different. They can be Raw, SDTM, and ADaM dataset. For big assets, two deliverables (draft and final) are recommended. Draft deliverable should be provided to the project team a few weeks prior to the DLP. The project team can review the draft

deliverable and provide comments for the DSUR programming team to incorporate if needed. The DSUR Programming team plans for the data extraction and achieves the data snapshot. Based on the data snapshot, the DSUR programming team produces final deliverable and sends them to the project team for review. Once the final deliverable has been reviewed, the DSUR programming team compiles unique outputs across the studies for DSUR regional appendices. Finally, it loads DSUR outputs to eCTD dossier system and notifies the regulatory team.
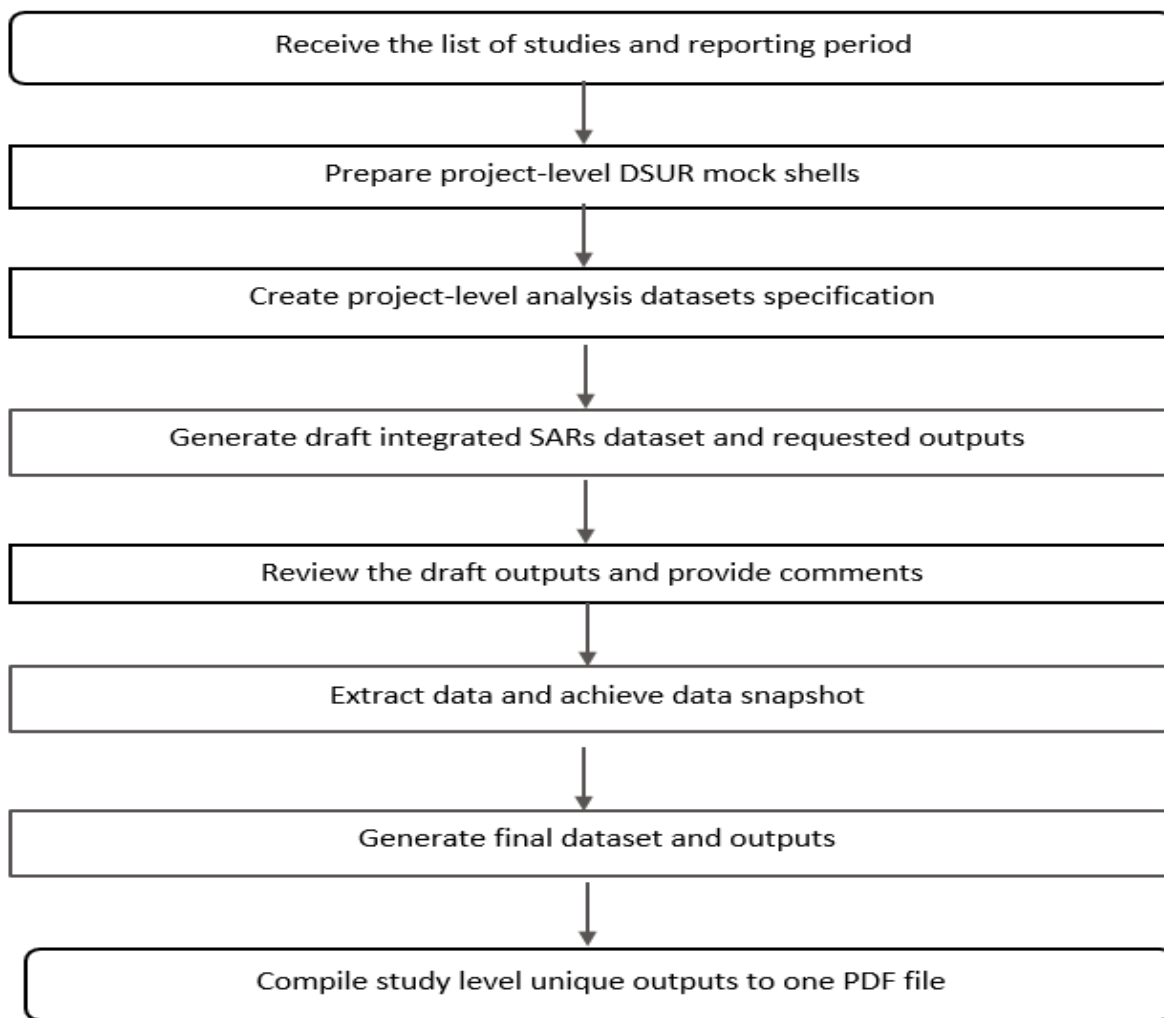
```
┌─────────────────────────────────────────────────────────┐
│        Receive the list of studies and reporting period   │
└─────────────────────────────────────────────────────────┘
                            │
                            ▼
┌─────────────────────────────────────────────────────────┐
│            Prepare project-level DSUR mock shells          │
└─────────────────────────────────────────────────────────┘
                            │
                            ▼
┌─────────────────────────────────────────────────────────┐
│         Create project-level analysis datasets specification│
└─────────────────────────────────────────────────────────┘
                            │
                            ▼
┌─────────────────────────────────────────────────────────┐
│      Generate draft integrated SARs dataset and requested outputs│
└─────────────────────────────────────────────────────────┘
                            │
                            ▼
┌─────────────────────────────────────────────────────────┐
│          Review the draft outputs and provide comments     │
└─────────────────────────────────────────────────────────┘
                            │
                            ▼
┌─────────────────────────────────────────────────────────┐
│            Extract data and achieve data snapshot          │
└─────────────────────────────────────────────────────────┘
                            │
                            ▼
┌─────────────────────────────────────────────────────────┐
│              Generate final dataset and outputs            │
└─────────────────────────────────────────────────────────┘
                            │
                            ▼
┌─────────────────────────────────────────────────────────┐
│          Compile study level unique outputs to one PDF file│
└─────────────────────────────────────────────────────────┘
```

Figure 1 Workflow for creating DSUR outputs

DSUR REGIONAL SPECIFIC LISTINGS

As per the guidance for industry E2F development safety update report, the programming team is responsible for generating both cumulative and within reporting period outputs for DSUR. For the cumulative tables, all data need to be reported since the Development International Birth Date (DIBD). The cumulative outputs of estimated cumulative subject exposure tables and cumulative serious adverse events tables are required. For reporting period outputs, only the data that occurred during the reporting period is required. The reporting period listings are list of subjects who died during the reporting period (Display 1) and list of subjects who dropped out of clinical trials in association with an adverse event during the reporting period (Display 2). These listings need to be included in the region-specific appendix of the

DSUR report. The list of subjects who died during the clinical trials should include the following information: subject information, assigned treatment (could still be blinded), first dose date, last dose date, death date and cause of death.

```
                              Death Listing
                  Reporting Period 04JUL2021 to 03JUL2022

Treatment Group: Blinded
-----------------------------------------------------------------------------------------

Unique Subject ID     Randomization First Dose  Last Dose            Days Since
  (Age/Sex/Race)      Date          Date        Date     Death Date  Last Dose  Cause of Death    Specify
-----------------------------------------------------------------------------------------

TAxxxxxx-xx-xx        06APR2016     06APR2016    02APR2018 27OCT2021  1305       DISEASE
  (67/M/C)

-----------------------------------------------------------------------------------------
A=Asian, B=Black/African American, C=White, I=American Indian/Alaska Native, O=Other, P=Native Hawaiian/Other Pacific Islander
M=Male, F=Female, U=Unknown
Program Source: /xxx/prog/listings/rl-dt.sas                                        07JUL2022:11:18:02
```

Display 1 Sample list of subjects who died during the reporting period

The list of subjects who dropped out of clinical trials with an adverse event during the reporting period should include all subjects who dropped out of clinical trials in association with adverse events during the reporting period, whether or not it is drug-related. The following information should be included in this listing: Subject information, AE information from AE CRF page including AE onset date, AE resolution date, AE term, Severity, Relationship, Action, Outcome and so on.

```
        List of subjects who dropped out of clinical trials in association with an adverse event
                          Reporting Period 04JUL2021 to 03JUL2022
Treatment Group: Blinded
-----------------------------------------------------------------------------------------

                         Onset D/T        DUR      System Organ Class
Unique Subject ID   Period  Resolution D/T  TRD        Preferred Term                 REL     TRT
  (Age/Sex/Race)    Visit     Study Day     Type       Reported Term                  CTC     ACT
-----------------------------------------------------------------------------------------

TAxxxxxx-xxx-xxxx   FOLLOW-UP  13JUL2021/18:41  42.9H  Vascular disorders             6       1
  (48/M/C)          FOLLOW-UP  15JUL2021/13:34  19D      Peripheral embolism          3       6
                               1527             SAE        THROMBOEMBOLISM OF RIGHT ARM

-----------------------------------------------------------------------------------------
MedDRA: 25.0
A=Asian, B=Black/African American, C=White, I=American Indian/Alaska Native, O=Other, P=Native Hawaiian/Other Pacific Islander;
M=Male, F=Female, U=Unknown
DUR (DURATION OF EVENT)/ TRD (TIME RELATIVE TO MOST RECENT DOSE): D = DAYS  H = HOURS  M = MINUTES  S = SECONDS
REL (RELATIONSHIP): 5 = NOT RELATED   6 = RELATED; TRT (TREATMENT REQUIRED): 0 = NO   1 = YES
ACT (ACTION): 1=DOSE NOT CHANGED  2=DOSE REDUCED 3=DOSE INCREASED 4=DOSE DELAYED 5=DRUG INTERRUPTED 6=DRUG WITHDRAWN
CTC (COMMON TERMINOLOGY CRITERIA): 1 = GRADE 1   2 = GRADE 2   3 = GRADE 3   4 = GRADE 4   5 = GRADE 5
Program Source: /xxx/prog/listings/rl-ae.sas                                         07JUL2022:11:18:12
```

Display 2 Sample list of subjects who dropped out of clinical trials in association with an adverse event during the reporting period

PDF CONVERSION AND COMBINATION TOOL

Subject level analysis datasets (ADSL & ADAE) are used to generate the two listings, and SAS listing with the file extension ".lst" is easily produced by using "PROC REPORT". The naming convention for the AE listing is rl-ae-discTAxxxxxx, and the naming convention for death listing is rl-dt-deathTAxxxxxx, where TAxxxxxx is the study number. After review by each study team, DSUR programming team will combine the study level outputs into one PDF file for DSUR regional appendices. This utility %BLS2PDF macro is used to convert and combine sets of existing listings into a consolidated PDF file that comply with submission requirement PORTABLE DOCUMENT FORMAT SPECIFICATIONS (fda.gov). For example, if there are 10 studies (Study TA001001 - Study TA001010) for a particular asset, 2 listings of rl-ae-discTAxxxxxx and rl-dt-deathTAxxxxxx will be generated for each study, thus there are 20 listings in

total. This utility will combine 10 AE listings from 10 studies into one PDF file (Display 3) and combine 10 death listings from 10 studies into another PDF file. The pdf file containing the combined study-level outputs are bookmarked, which enables users to quickly find the studies they are interested in.

Display 3 Combined PDF file for AE leading to discontinuation listing

1. Macro %BLS2PDF

%BLS2PDF macro has following features.

A. Efficient Documentation Generation

- Batch converts multiple .lst files into a unified PDF document through a single macro call.
- Automatically generates bookmarks for easy navigation.
- Orders tables, listings, and bookmarks based on their IDs, eliminating any manual organization.
- Allows grouping of bookmarks by adding top-level bookmarks and forming a multi-level bookmark tree.

B. Customizable Input File Selection

- Allows selection of specific subsets of .lst files through file choosers that support wildcard characters (*, :, or ?).
- Offers content-based file selection through filters on table/listing IDs as prefixes.

C. High Performance and Platform Independence

- Works on both Batch SAS and SAS Studio platforms and supports both Wlatin1 and Unicode encodings.
- Processes large numbers of tables or listings (1000+) in a short amount of time.

D. Trouble-Free Operation

- Performs a sanity check on all macro parameters.
- Reports any abnormal tables and listings based on metadata from cover pages.
- Cleans up all temporary datasets after macro call(s) are completed, ensuring worry-free operation.

2. Macro parameters

%BLS2PDF Macro Parameters are listed in Table 1:

Parameter	Meaning	Example
Required Parameters		
DIR=	Directory for the BMS-style .lst files to be converted and combined	DIR=*/gbs/…/input_lst*
Important Optional Parameters		
OUT_PDF=	Name of the output all-in-one PDF file. If blank, each of .lst files in the directory will be converted into a corresponding PDF file.	OUT_PDF=*all-in-one.pdf*
KEEP=, and DROP=	The file choosers, which allow you to choose subsets of table/listing files by their file names with 3 wild characters (*, :, and ?)	Default: Keep= *.lst For example: KEEP=rt*.lst rl-*.lst, Drop= rt-abc*.lst
IDS=	The content filters, which allow you to choose subsets of tables or listings by the contents in their IDs. They are executed after the file choosers. Note the contents are case-sensitive ,working as prefixes.	For example, IDS="Appendix 16.1.2" "Appendix 16.3" IDS="Table 14.1" "Table 14.3.1"
Useful Optional Parameters		
TOPBM=	Label for the top-level bookmark to be added to the final output PDF file	TOPBM=%str(Analysis Table)
OUT_DIR=	Output directory for the all-in-one PDF file.	Default: OUT_DIR= &DIR For example: OUT_DIR==*/gbs/…/output*
Encoding=	Encoding (Unicode vs. Wlatin1) used in BMS .lst files	Default: the encoding used by current SAS session. Note: Batch SAS uses WLATIN1 while AWS SAS Studio uses UNICODE.
OPTS=	Options. The 8 options are supported CovPage: Include cover page NoCovPage: or Exclude cover page NoDocID: A bookmark is consisted of ID and titles. OnlyDocID: A bookmark is consisted of DocID only PreDocId: A bookmark is consisted of DocID, ID and titles	Default: OPTS=CovPage NoDocID Note: Optional values are always case-insensitive. Using mixed cases in option values will improve the readability.

	PostDocID: A bookmark is consisted of ID, titles and DocID ADDTID or NoAddTID: Add Table ID (or Listing ID) to the top of each page, or No action	

Table 1 Macro parameters

3. Example program to call %BLS2PDF

%BLS2PDF can be simply called after storing it in a sasautos library. Here is an example to convert and combine a set of .lst files starting with rl-ae-disc into a PDF file with the name of dsur-aedisc.pdf:

```
%BLS2PDF(dir = /gbs/prod/clin/programs/ca/dsur/2022/rpt/output
        ,keep = rl-ae-disc*.lst
        ,out_pdf = dsur-aedisc.pdf);
```

4. Technique & mechanism for implementation

The implementation of %BLS2PDF macro is comprised of two key components: the first component reads in sets of .lst files and extracts the metadata from each file, while the second component sorts the files, converts them into a single PDF document and at the same time generates bookmarks. The following is a typical piece of the SAS code:

Part 1. convert a set of .lst files into a dataset

/* 1. Read the contents of the .lst file */

```
data inf&id;
   length line $2048  fpath $1024;
   retain lineno 0 pageno 0;
   fpath="&fullpath";  /* fullpath contains lst file location and name */
    if fileexist(fpath) then do;
      infile "&fullpath" end=last missover dlm="09"x;
      fileID=&id;
    end;
    else do;
      putlog;
      putlog "Er%str()ror: the .lst file [[&fullpath]] does not exist!";
      putlog;
      stop;
    end;
    input;
    line=_infile_; lineno=LineNo+1;
    /* Handle encoding */
    %if "%upcase(&encoding)"="UTF-8" %then %do;
        line=kcvt(Line,"UTF-8", "wlatin1");
    %end;
       if substrn(line,1,1)="0C"x then do;
          pageno=pageno + 1; lineno=1;
          line=substrn(line,2);
       end;
run;
```

/* 2. Combine single datasets into one dataset */

```
data all;
   set
```

```
      %do id = 1 %to &total;  /* total number of lst files */
          inf&id.
      %end; %str(;)
   run;
```

Part 2. Create all-in-one PDF file with bookmarks from the combined dataset in Part 1

```
   ods pdf file="&out_pdf"
      startpage=yes style=Styles.eSUBPDFL bookmarkgen=yes compress=6
      contents=off;
   %do id=1 %to &total;
        %let bookmark=;
        data _null_;
           set all(where=(fileid=&id))
              Call symputx("bookmark", strip(fileid)||":"||strip(title));
        run;
        ods proclabel="&bookmark";
        proc report data=all(where=(fileid=&id)) nowd headline noheader
                style(REPORT)=[outputwidth=95%] contents="";
           column pageno line;
           define pageno/order noprint;
           define line /display "line contents" width=132 flow;
           break after pageno/page;
        run;
     %end;
     ods pdf close;
```

CONCLUSION

This paper describes DSUR submission process and presents a powerful tool that can be used to combine and convert individual study listings into all-in-one bookmarked PDF file for submission. This tool not only can be used for DSUR reporting, but also for other reporting purposes such as IND safety report, site level listings and CSR appendices. It greatly simplifies and speeds up the generation of reports that require multiple-level bookmarks organization in regulatory submission processes.

REFERENCES

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https://www.fda.gov/media/71255/download

FDA Technical Specifications Document - PDF specifications

PORTABLE DOCUMENT FORMAT SPECIFICATIONS (fda.gov)

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