

# A Well Designed Process and QC Tool for ISS Reports

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## ABSTRACT

The ISS (Integrated Summary of Safety) is a key component in submissions for drug approvals in the pharmaceutical industry. This report consists of multiple reports from clinical studies that focus on drug safety and are generally programmed in SAS®. The ISS uses relevant data from one or more clinical studies to generate tables and figures from integrated data. Various methods are used to verify the results found on the ISS reports. One method focuses on whether the ISS analysis results from the integrated data are consistent with the results from each of the individual studies. This paper introduces a well-designed process and validation tool to ensure the output consistency and integrity of the ISS reports with the individual underlying studies.

## KEYWORDS

ISS, ISE, SASHELP VTABLE, PROC COMPARE, QC

## INTRODUCTION

As a critical component of the safety submission, the ISS (Integrated Summary of Safety) report is required by the U.S. Food and Drug Administration. An ISS report summarizes relevant data from more than one clinical study and includes tables and figures generated from integrated datasets. People use various methods to verify the counts shown in ISS reports - it is highly important that the ISS analysis results from the integrated datasets are consistent with the results from the individual studies. This paper introduces a well-designed process and validation tool to ensure consistency and integrity of the output.

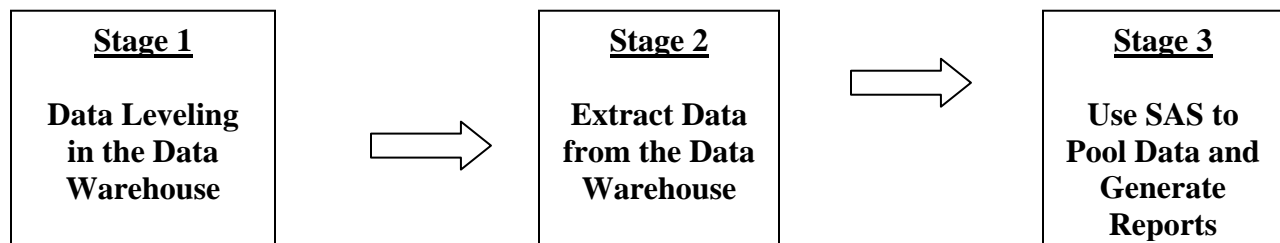
## ISS REPORTS

Per FDA guideline documents, "Guideline for the format and content of the clinical and statistical sections of an application", (FDA, July 1988), section H (21 CFR 314.50 (d) (5) (vi) (a)), the important information for a submission includes overall extent of exposures, demographic and other characteristics of the study population, adverse experience in clinical trials, clinical laboratory evaluation in clinical trials, etc. When pharmaceutical companies are filing safety submissions to FDA, usually the ISS reports include the following tables: extent of population exposure, deaths, serious adverse events, nonfatal serious adverse events, dropouts due to adverse events, drug related adverse events, common adverse events, laboratory abnormalities which lead to termination, vital sign, demographic and baseline features of individual patients. In addition, some other related tables such as concomitant medication, prior therapy, disposition of patients who entered the trial typically may be included in the analysis.

Notice that the ISS is a new analysis, not simply a summary of individual protocols. An integrated overall view is needed and hence these tables are generated based on integrated data pooled from multiple studies. In order to guarantee the consistent use of the same adverse event dictionary term, the adverse events term from each individual protocol should be leveled to same version of MedDRA (Medical Dictionary for Regulatory Activities). MedDRA is a clinically validated international medical terminology used by regulatory authorities and the pharmaceutical industry.

## THE PROCESS DESIGN

The process of an ISS project can be divided into three stages; first, data leveling to most recent updated MedDRA version in a data warehouse; second, extracting data from the data warehouse; and third, generating those required tables per 21 CFR 314.50 (d) (5) (vi) (a).



A decision should be made regarding when to pool the multiple studies data into one ISS dataset. This paper suggests pooling the data at stage three. Since the ISS datasets tend to have big file sizes, pooling data at an early stage would slow

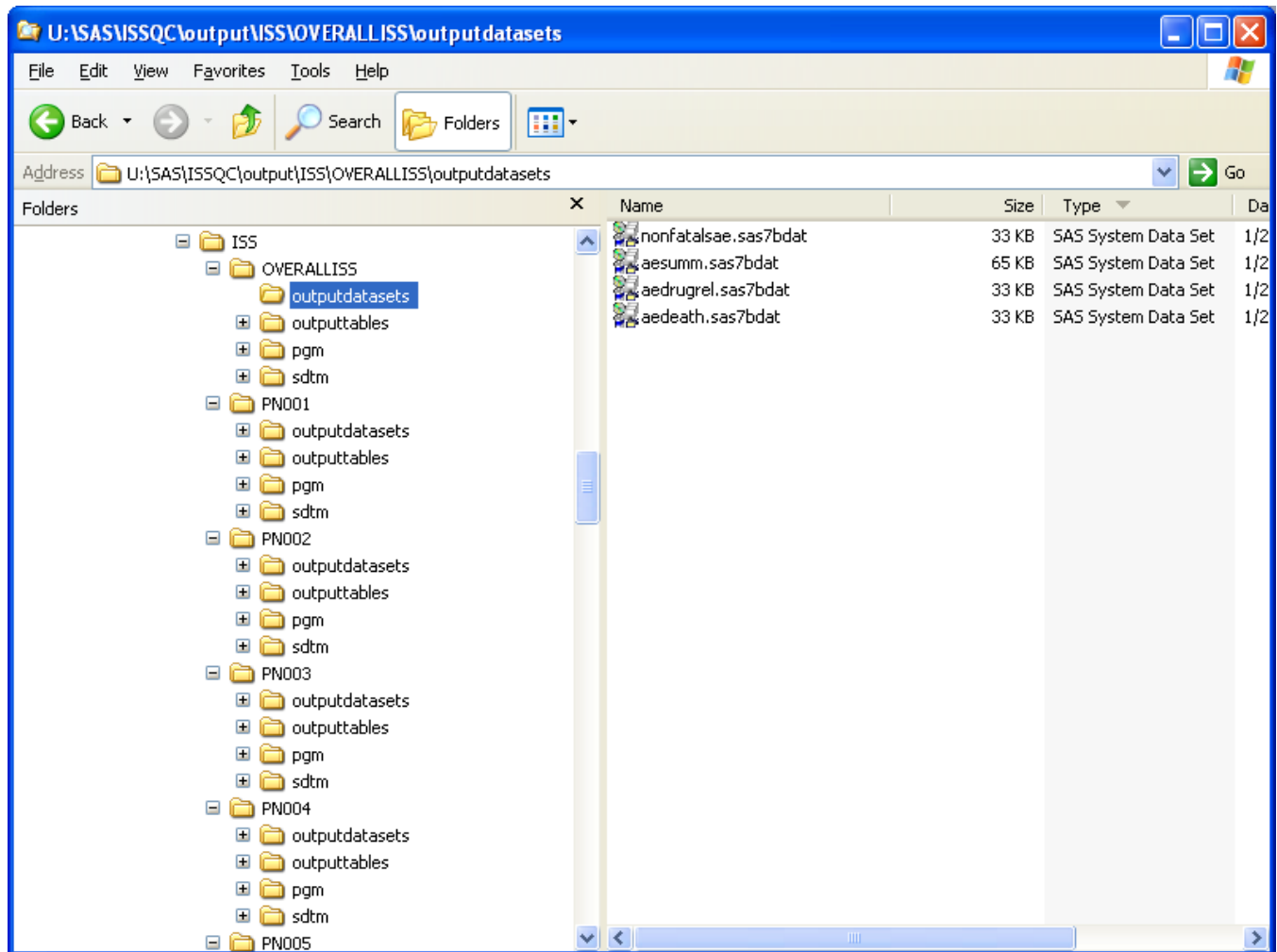
down the computer processing time. Another advantage of extracting individual study data first and afterward pooling data in SAS is that the results from each of the individual studies can be easily verified.

A logical folder structure to support this decision process is described next. The working folder is designed to be one ISS folder containing all pooled studies and several individual protocol folders. Each folder contains an identical structure of subfolders. The individual study datasets are stored under their respective individual study subfolders.

When generating output tables, a SAS dataset is generated as well to store the table counts.

The ISS dataset is created by pooling all individual study datasets into one dataset. Based on this ISS dataset, the required tables are created as well as the output datasets which store the table counts.

The folder structure is as follows.



## TOOLS: SASHELP Dictionary Views

SAS sessions provide DICTIONARY, a reserved LIBREF, that stores metadata of the data at run time. The DICTIONARY LIBREF can only be used with PROC SQL. SAS users can either use PROC SQL to create a view from DICTIONARY metadata, or use the SAS provided SASHELP views. These SASHELP views are helpful tools because they are relatively smaller in size compared to DICTIONARY tables which makes it more efficient to check the metadata of the SAS datasets.

This paper uses the SASHELP.VTABLE view as the main tool to check the datasets.

SASHELP.VTABLE: Contains information for all defined SAS datasets stored in the defined LIBNAME.

## IMPLEMENTATION AND ALGORITHM

ISS analysis can involve many protocols and at the same time hundreds of tables may be generated for one ISS project. Manually entering hundreds of file names into the SAS code to accomplish QC checking is not an ideal approach. There is a need to automate the process so that all output dataset file names for the ISS folder and each protocol folder are read automatically via SAS.

### **Step 1: Use SASHELP.VTABLE to read in the SAS output dataset name**

This code below uses the SASHELP.VTABLE view to retrieve records from the specified LIBNAME value. Variable MEMNAME stores the output dataset name for the selected LIBNAME folder.

```
*** read ISS folder ***

    libname iss "&isslib";

    data isstable(keep=memname);
        set sashelp.vtable( where=(libname="ISS" ) );
        run;

*** read individual protocol folder ***
    libname prot1 "&protlib1";
    data protlib1 (keep=memname);
        set sashelp.vtable( where=(libname="PROT1" ) );
        run;

.
.
.
```

### **Step 2: Identify the ISS table ready for QC**

In some cases if at least one individual protocol does not have a specific table generated, the QC cannot be done. The following code illustrates how this step identifies the files which exist in each folder. Note that the QC can only be done when the tables are generated in both the ISS folder and each individual protocol folder.

```
data match misscomp;
    merge isstable(in=in0)
          protlib1(in=in1)
          protlib2(in=in2)
          protlib3(in=in3)
          protlib4(in=in4)
    ;
    by memname;
    a = in0;
    b = in1;
    c = in2;
    d = in3;
    e = in4;
    if min (a, b, c, d, e)=1 then output match;
    else if a=1 then output misscomp;
run;
```

### **Step 3: Check the data consistency**

It is important that the ISS analysis results from the integrated datasets are consistent with the results from each of the individual studies. When ISS output table datasets exist and each protocol output table datasets exist as well, check whether the sum of the counts from each protocol output table datasets equals the ISS output table dataset counts.

The syntax below directs SAS to go through all SAS datasets that exist in all folders identified in Step 2. The variable EXAMPARM represents the AE preferred term and the variable BODY\_SYS is the AE System Organ Class. The DATA step illustrates the merge ISS AE table output dataset with all individual study output datasets by AE System Organ Class and AE preferred term. Next, the IN operator is used in conjunction with the dataset counts to compare overall ISS counts with the

sum of all individual study counts. Only when the sum of individual results equals the ISS counts, can it be concluded that the integrated result is consistent with the individual studies data.

In case of discrepancy, further investigation should be made in two aspects: first, whether all studies has been leveled to the same MedDRA version; second, whether a different set of criteria was applied when retrieving individual study data to create the ISS reports. The different criteria could be the following and not limited to: different definition of population, different definition of post treatment period.

```
proc sql noprint;
  select count(memname) into :tot
  from match
  ;
quit;

%let tot=&tot;

proc sql noprint;
  select memname into :tabname1 - :tabname&tot
  from match
  ;
quit;

%do _j=1 %to &tot;
  proc sort data=iss.&&tabname&_j out=iss;
    by examparm body_sys;
  run;

  proc sort data=prot1.&&tabname&_j out=prot1;
    by examparm body_sys;
  run;

  proc sort data=prot2.&&tabname&_j out=prot2;
    by examparm body_sys;
  run;

  proc sort data=prot3.&&tabname&_j out=prot3;
    by examparm body_sys;
  run;

  proc sort data=prot4.&&tabname&_j out=prot4;
    by examparm body_sys;
  run;

  data check;
    merge iss
      prot1 (in=in1 rename=(n1=n1_1 n2=n2_1 s1=s1_1 s2=s2_1) )
      prot2 (in=in2 rename=(n1=n1_2 n2=n2_2 s1=s1_2 s2=s2_2) )
      prot3 (in=in3 rename=(n1=n1_3 n2=n2_3 s1=s1_3 s2=s2_3) )
      prot4 (in=in4 rename=(n1=n1_4 n2=n2_4 s1=s1_4 s2=s2_4) )
    ;
    by examparm body_sys;
    if in1=1 and in2=1 and in3=1 and in4=1 and n1 ne sum(n1_1, n1_2, n1_3, n1_4)
      then n1_flag = 1;
    else n1_flag=0;
    .
    .
    .
  run;

  proc print data=check;
    where n1_flag=1 ;
    var examparm body_sys n1_flag n1; ;
    title "The sum of individual protocols does not equal to the pooled
```

```

protocols";
title2 "&&tabname&_j";
run;

```

## OUTPUT

The QC tool for this paper lists out the following:

- tables which are missing in at least one individual study (the intermediate dataset MISSCOMP from step 2)

Obs	MEMNAME	MISSINGP
1	AEDEATHNR	001 002 003
2	AEDEATHR	001 002 003 004
3	AEDRUGRELOPCTNR	001
.		
.		
.		

The missing output dataset from individual studies should be created in order to perform full QC.

- A summary result is provided here for those tables which can be QC'd. The ISS example in this paper has two treatment arms. Variable N1\_FLAG and N2\_FLAG are the flag variables which indicate the comparison result of numerator counts from treatment arm 0001 and 0002, respectively. Variable S1\_FLAG and S2\_FLAG are the flag variables which indicate the comparison result of denominator counts from treatment arm 0001 and 0002, respectively. This summary result can quickly navigate which tables pass the QC and which need further investigation. The TBLNAME with warning flag value equal to 1 means it does not pass the QC. For example, AE specific tables (AESPECIFIC0PCTNR and AESPECIFIC0PCTR), do not pass QC.

Obs	TBLNAME	N1_FLAG	N2_FLAG	S1_FLAG	S2_FLAG
1	AESOC0PCTNR	0	0	0	0
2	AESOC0PCTR	0	0	0	0
3	AESPECIFIC0PCTNR	0	0	1	1
4	AESPECIFIC0PCTR	0	0	1	1
5	AESUMMNR	0	0	0	0
6	AESUMMR	0	0	0	0

- For those tables with warning flag equal to 1, the SAS code would automatically print out the records which do not match with individual studies. The following case shows that the ISS table has 318 patients with no AE in arm 0002 but the sum from individual studies is 320. On the other hand, the ISS table has 329 patients with AE in arm 0002 but the sum from individual studies is 327. These discrepancies suggest that either the ISS table or any one protocol has a different set of criteria.

E		B							
X		O		S					S
A		D		2					2
M		Y		—					—
P		—		F	S	S	S	S	F
O	A	S		L	2	2	2	2	L
b	R	Y		A	S	—	—	—	A
s	M	S		G	2	1	2	3	4
448 with no specific adverse events		subjects with no adverse events		1	318	82	37	119	82
450 with one or more specific adverse events		subjects with adverse events		1	329	96	17	140	74

## CONCLUSION

When large number of studies are included in an ISS and large numbers of tables are requested, the verification job to ensure the output consistency and integrity of the ISS reports with the individual underlying studies can be labor intensive and tedious. Using SAS to automatically QC the results and drill down to the problem record and treatment arm level is a wise way to proceed. As long as the ISS folders and individual protocol folders have been designed to be identical in structure, the QC tool introduced in this paper can easily be used and reused in other ISS projects and other projects involving integrated data.

## REFERENCES

- "Guideline for the format and content of the clinical and statistical sections of an application", (FDA, July 1988)

## ACKNOWLEDGMENTS

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