A Drug Safety Reporting System in SAS®

Yang Wang, Seattle Genetics, Seattle, WA
Shawn Hopkins, Seattle Genetics, Seattle, WA
Norm Fox, Seattle Genetics, Seattle, WA
Raghu Kumbharathi, Seattle Genetics, Seattle, WA
Tom Hunter, Seattle Genetics, Seattle, WA

ABSTRACT

SAS® is traditionally used as a primary programming language to report trial data from clinical studies. It is used in generating data sets, tables, listings and figures designed to answer study questions on safety and efficacy of the drug during clinical trials. This paper introduces a flexible reporting system that leverages the power of SAS®, clinical reporting infrastructure and resources at Seattle Genetics to provide programming solutions in an unconventional setting.

INTRODUCTION

The drug safety system collects Serious Adverse Reactions (SAR) from Clinical Studies, Investigator Sponsored Trials, Post Marketing Surveillance and Spontaneous Reports. The primary function of the database is to collect and submit individual case reports to the FDA and other regulatory authorities. When a drug gains marketing authorization, the database contains a comprehensive list of all sources of adverse reactions, and becomes the primary tool for safety analysis and signal detection. In addition, other aggregate reports and business reports are generated for various user groups.

Traditionally, many pharmaceutical companies use analytical tools (e.g. Business Objects, Cognos) to supplement aggregate reports embedded in their drug safety systems. This setup requires a separate infrastructure and skill set in order to develop and process reports. Typically, the systems are feature rich for developing queries and formatting reports but do not include much programming to automate tasks. Seattle Genetics' Oracle Argus Safety database system (Drug Safety System) is hosted by an outside vendor. The challenges and cost of implementing the traditional tools with a hosted system necessitated an alternative for aggregate report generation. A process was put in place to extract the Oracle database behind the Drug Safety System into SAS® datasets and leverage the current clinical reporting infrastructure in SAS® to support reporting from the Drug Safety System.

METHODS

1. PROCESS SUMMARY

SAS
Dataset Transfer

Data Transfer
QC

Analysis
Dataset
Generation & QC

Output
Generation
and QC

Report
Distribution
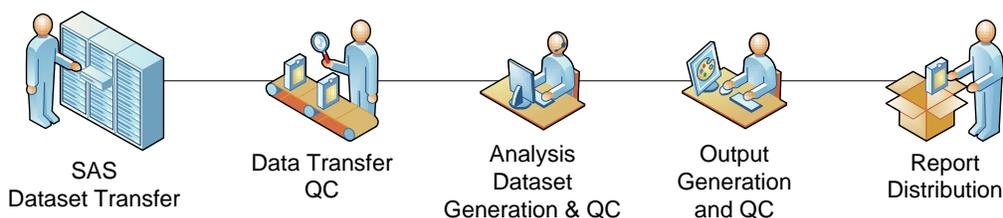
Figure 1. The safety reporting process is illustrated in the following steps: 1) obtain data from the host company. 2) verify data are both current and that there are no unexpected changes to structure and certain tables. 3) generate and QC analysis data sets 4) generate and QC output files 5) distribute reports.

2. DATA TRANSFER AND QC

This Drug Safety System sits on top of a highly normalized Oracle Database. The data transfer from our host system contains the raw data in SAS datasets from the Oracle database. Once the data are downloaded, a data QC program is run that verifies the currency of the data along with ensuring that the structure and other data elements have not changed.

3. CREATE A COMMON POOL OF ANALYSIS DATASETS

Part of handling raw data is reformatting the data to make it easier to generate and analyze data. For example, The Oracle Database behind our Drug Safety System contains rows that have been flagged as "deleted" by users. These data points are part of the systems required audit trail, but are not considered valid for reporting purposes. Based on user requirement, specifications are drafted to support programing and validation of 5 datasets from the 332 raw datasets. The derived datasets contain ~95% of the fields used in reporting. This approach helps to leverage a common pool of analysis data sets for multiple reports.

Figure 2. Exclude rows flagged as "deleted" in database in analysis datasets.

4. REPORT GENERATION AND QC

With the Global Safety group, deliverables are differentiated into two categories by validation requirements:

1. Regulatory submissions – output that is generated as part of a regulatory submission (e.g see the PBRER example below)

2. Scheduled Business reports and others –outputs that are regularly delivered to users on a scheduled basis. (e.g see Compliance Report below)

The same approach and processes are used for generating output from the Drug Safety System as the clinical database output. Share global macros such as our library of output generation templates to cut down on programming time. The directory architecture allows all active reports to share the most current downloaded data. For regulatory submissions and key business reports, the output is archived by copying the versions of the data and utilities used to generate the outputs to the appropriate folder and write access is removed.
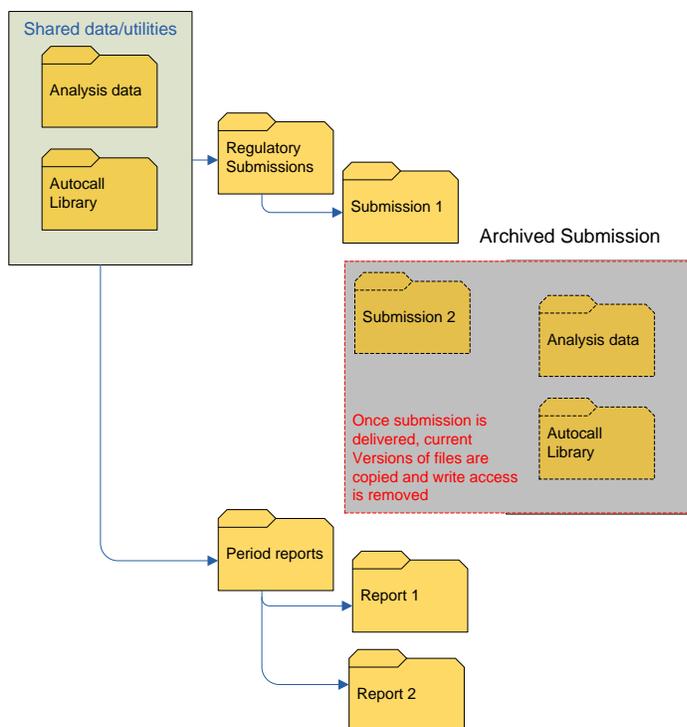
Figure 3. Directory structure.

5. AUTOMATE REPORT DISTRIBUTION

The Report Distribution Utility automates the distribution of periodic safety reports to internal and external clients. The utility consists of:

- An HTML application that provides a user interface to the utility and allows users to select reports for delivery.
- A SAS program that moves the files from the SAS fileshare to the shared server and email distribution server.
- Software that reads email requirements from SAS and generates emails to internal and external recipients via corporate exchange server.
- A command-line sFTP tool that transfers SAS datasets to external recipients.
- A database that defines the details (content, schedule, recipients, etc.) for each period deliverable.

The application reads in the database file that identifies the available reports and their standard distribution timelines. The user can send the reports due for that day, or select a custom subset of reports. When the user clicks "Send" in the user interface, the SAS program moves the report objects to the shared server and email server. The SAS program calls the email generation software via PROC HTTP, passing the definition of each email's content. The application creates the email with attachments for external recipients, and attachments and/or hyperlinks to the shared server for internal recipients. A log detailing the distribution is generated, and the status (success/failure) of each report distribution is relayed back to HTML application user interface.
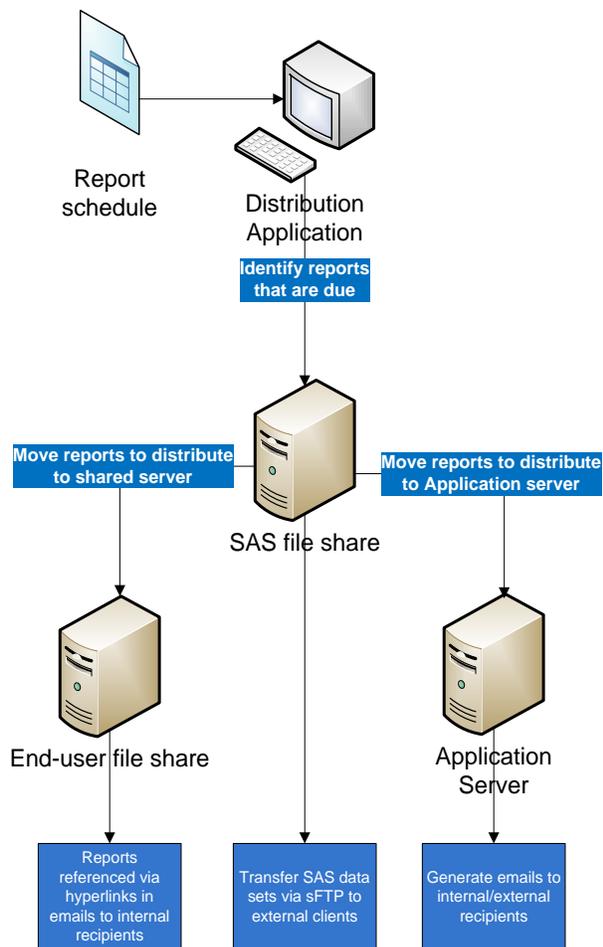
Figure 4. This diagram illustrates the automated report distribution process.

EXAMPLES OF SAFETY REPORTS

Regulatory Reports: Regulatory report examples Include Periodic Benefit Risk Evaluation Report (PBRER) and Development Safety Update Report (DSUR). These reports are required by global regulatory agencies. Following are examples of two outputs that are part of the PBRER: Aggregate data for SAEs from clinical and AEs from Post-Marketing Sources. Many reports use the same macros to output tables in rich text format based on the infrastructure developed for clinical reporting.

Company: Seattle Genetics

Cumulative Tabulations of Serious Adverse Events from Clinical Trials

01JAN13:00:00

System Organ Class Preferred Term	Study Drug	Blinded	Active Comparator	Placebo
System Organ Class 1	XX	XX	XX	XX
Preferred Term 1	XX	XX	XX	XX
Preferred Term 2	XX	XX	XX	XX
Preferred Term 3	XX	XX	XX	XX
Preferred Term 4	XX	XX	XX	XX
Preferred Term 5	XX	XX	XX	XX
Preferred Term 6	XX	XX	XX	XX
Preferred Term 7	XX	XX	XX	XX
Preferred Term 8	XX	XX	XX	XX
Preferred Term 9	XX	XX	XX	XX
Preferred Term 10	XX	XX	XX	XX
Preferred Term 11	XX	XX	XX	XX
Preferred Term 12	XX	XX	XX	XX
Preferred Term 13	XX	XX	XX	XX
Preferred Term 14	XX	XX	XX	XX
Preferred Term 15	XX	XX	XX	XX
Preferred Term 16	XX	XX	XX	XX

Page 1 of X

CONFIDENTIAL
Extract Date: 01JAN13
Source: O:\Biostatistics\GSDB\...\t-pbrer-sae-cum.sas Output: t-pbrer-sae-cum.rtf (01JAN13:00:00) Dataset: xxxx

Figure 5. Aggregate Reports for SAEs from clinical trials.

Company: Seattle Genetics

Numbers of Adverse Drug Reactions by Preferred Term from Post-Marketing Sources

01JAN13:00:00

System Organ Class Preferred Term	Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing study and reports from other solicited sources	
	Serious		Non Serious		Cumulative All	Serious	
	Interval	Cumulative	Interval	Cumulative		Interval	Cumulative
System Organ Class 1	XX	XX	XX	XX	XX	XX	XX
Preferred Term 1	XX	XX	XX	XX	XX	XX	XX
Preferred Term 2	XX	XX	XX	XX	XX	XX	XX
Preferred Term 3	XX	XX	XX	XX	XX	XX	XX
Preferred Term 4	XX	XX	XX	XX	XX	XX	XX
Preferred Term 5	XX	XX	XX	XX	XX	XX	XX
Preferred Term 6	XX	XX	XX	XX	XX	XX	XX
Preferred Term 7	XX	XX	XX	XX	XX	XX	XX
Preferred Term 8	XX	XX	XX	XX	XX	XX	XX
Preferred Term 9	XX	XX	XX	XX	XX	XX	XX
Preferred Term 10	XX	XX	XX	XX	XX	XX	XX
Preferred Term 11	XX	XX	XX	XX	XX	XX	XX
Preferred Term 12	XX	XX	XX	XX	XX	XX	XX
Preferred Term 13	XX	XX	XX	XX	XX	XX	XX

Page 1 of X

CONFIDENTIAL
Extract Date: 01JAN2013
Source: O:\Biostatistics\GSDB\...\t-pbrer-ae-post.sas Output: t-pbrer-ae-post.rtf (01JAN13:00:00) Data:xxxx

Figure 6. Aggregate Reports from Post-Marketing Sources.

Drug Safety and Medical Monitor Reports: These reports are sent to the internal risk management group and medical monitors. The following is an example of cumulative AE frequency Table from Signal Detection Report.

Company: Seattle Genetics

Cumulative AE Frequency Table for Non-Spontaneous Cases until JAN2013

		Unblinded					Blinded				
System Organ Class	**Preferred Term**	**S**	**NS**	**INI**	**Reporting %**	**Reporting Ratio**	**S**	**NS**	**INI**	**Reporting %**	**Reporting Ratio**
System Organ Class 1	Preferred Term 1	XX	XX	XX	.xx	.xx	XX	XX	XX	.xx	.xx
	Preferred Term 2	XX	XX	XX	.xx	.xx	XX	XX	XX	.xx	.xx
System Organ Class 2	Preferred Term 1	XX	XX	XX	.xx	.xx	XX	XX	XX	.xx	.xx
	Preferred Term 2	XX	XX	XX	.xx	.xx	XX	XX	XX	.xx	.xx
System Organ Class 3	Preferred Term 1	XX	XX	XX	.xx	.xx	XX	XX	XX	.xx	.xx
System Organ Class 4	Preferred Term 1	XX	XX	XX	.xx	.xx	XX	XX	XX	.xx	.xx
System Organ Class 5	Preferred Term 1	XX	XX	XX	.xx	.xx	XX	XX	XX	.xx	.xx
											Page 1 of 62

Extract Date: 01JAN2013
Event Count: Unblinded / Blinded XX / XX
Case Count for all AE's: Unblinded / Blinded XX / XX
Source: O:\Biostatistics\GSDB...\t-aefreq-nonspont.sas Output: t-aefreq-nonspont-cum.rtf (01JAN13:00:00) Data: xxxx

Figure 7. Example of Signal Detection Report. Reporting % is number of events per preferred term divided by total case of all preferred terms in the reporting period. Reporting Ratio is number of events per preferred term divided by total event count in the reporting period. S:Serious Event count, NS: Non-Serious Event count, INI: Case Count.

Business Reports: Below are two examples of regularly scheduled reports that are sent to various groups in clinical and drug safety operations. These reports either facilitate clinical trial conduct or track compliance with timelines. In Figure 5, a utility developed in SAS for clinical data reporting that does a dataset comparison and displays the changes between dataset versions were used. Figure 6 shows how the programming environment in SAS was used to run complicated custom date calculations and generate output as a figure and analysis table

	A	B	C	D	E	F	G	H	I
1	**Subject ID**	**Case Number**	**Case Status**	**Initial Receipt Date**	**Event Onset Date**	**Changes From Old Extract**	**Preferred Term**	**Reported Causality**	**Determi Causal**
2	xxxxx-xxxx	xxxxxxxxxxxx	File Room	DDMMM2013	DD-MMM-2013	Variables: Event Onset Date, Case Status	Preferred Term 1	Related	Related
3	xxxxx-xxxx	xxxxxxxxxxxx	Case Management	DDMMM2013	DD-MMM-2013	New AE	Preferred Term 2	Not Reported	Not Reporte
4	xxxxx-xxxx	xxxxxxxxxxxx	File Room	DDMMM2013	DD-MMM-2013	New AE	Preferred Term 3	Related	Related
5	xxxxx-xxxx	xxxxxxxxxxxx	Closed	DDMMM2013	DD-MMM-2013		Preferred Term 4	Related	Related
6	xxxxx-xxxx	xxxxxxxxxxxx	Closed	DDMMM2013	DD-MMM-2013		Preferred Term 5	Not Related	Not Related

Figure 8. Report used to reconcile SAE between safety database and study site. Note the "Change From Old Extract" will help site identify the changes and reconcile any SAE difference efficiently.

Month	No. cases and Sig Follow-ups	Late in X-report	Total Compliance%	Total due in 12-D	No. 12-D Late	12-D Compliance%	Total due in 9-D
JAN12	61	0	100	35	0	100	17
FEB12	110	0	100	41	0	100	56
MAR12	98	0	100	45	0	100	49
Total	869	0	100				

(Header spans: Percent Compliance)

Case Due Calculated	Workflow Due Date
Friday	Thursday
Weekend	Friday
Holiday	Day before
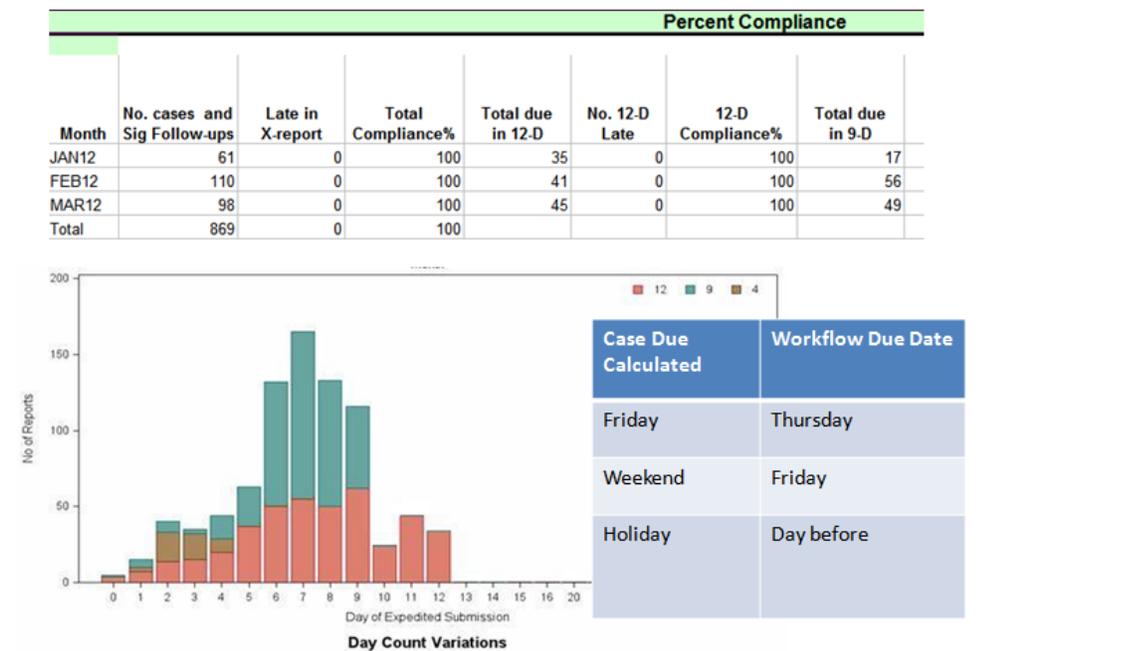
Figure 9. Report example of PVA specification, Compliance tracking with timelines and compliance percentage using mock data.

CONCLUSION

In a marketplace that has a plethora of off-the-shelf analytical and business intelligence tools, SAS® provides a powerful and flexible alternative. SAS® allows an existing clinical reporting infrastructure and skill set to be leveraged to support reporting from a Drug Safety System.

Future goals include harnessing the power of SAS® to eliminate the routine and tedious tasks to:

- Automate job process for periodic reports using system calls.
- Automate distribution of reports using an email system.

CONTACT INFORMATION

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

Name: Yang Wang
Enterprise: Seattle Genetics
Address: 21823 - 30th Drive S.E.
City, State ZIP: Bothell, WA 98011
Work Phone: 425-527-4354

E-mail: yawang@seagen.com

SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc. in the USA and other countries. ® indicates USA registration.

Other brand and product names are trademarks of their respective companies.