

Real Time Clinical Trial Oversight with SAS

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ABSTRACT

A clinical trial is an expensive and complex undertaking with multiple teams working together to accomplish study startup, conduct, data collection, monitoring and data cleaning. It is critical that the study is implemented as specified in the protocol and the data is clean and of good quality for a successful study. As most EDC systems are setup to export data as SAS datasets, a clinical programming team can easily leverage these datasets to provide the study team with metrics and tools to help focus and modulate monitoring and data cleaning efforts in real time.

INTRODUCTION

More often than not during study data analysis anomalies are encountered in the data that should have been resolved a long time before data base lock. This is especially a major problem for small pharma's where most of the work is outsourced and a library of standards is not in place to mitigate issues. In this scenario the clinical team conducting a trial needs access to the data on an ongoing basis to check for the health of the study and the quality of the data.

The paper presents a framework of tools developed in SAS, using periodic exports of the EDC (Electronic Data Capture) data during study conduct phase of the trial with the goal of providing the study team with real time feedback on study conduct, timely data entry and overall data quality. These tools comprise of a combination of excel work books and visualizations which are setup to run at a pre-specified times throughout the trial.

Tools developed comprise of [1] EDC data entry metrics to make sure the data is being entered into the database in timely manner to help generate queries and facilitate cleaning of the data. [2] Customized programmatic edits checks in an excel workbook with embedded links to the EDC system used by the data monitors for data driven monitoring and issuing queries. [3] Custom patient lifecycle graphical profiles for subjects with disposition events of interest.

Setup and Process

1. Export/download EDC data as SAS datasets.
2. Run the data through series of SAS macros.
3. Create excel workbooks/graphical output directly to a central location accessed by the study team.
4. Study team reviews and proceeds with action plan to mitigate issues.
5. Any new issues encountered are discussed and added to the macros for subsequent runs.
6. Repeat the above step 1-5 weekly.

Timely Data Entry Metrics

Timeliness of data entry into EDC by sites is very important. Data needs to be entered as soon as possible after a subject visit so that other downstream activities such as issuing queries for data cleaning, identifying safety signals and modulation of monitoring efforts can occur.

Timeliness of data entry can be monitored based on anchor of single data point entry for a visit or all data for a visit is entered or when all critical data has been entered into the EDC system. The approach in our case was to build a macro that was flexible enough to change the metrics based on any of the above 3 criteria. The metrics presented below are for phase 3 recruited surgery studies with IV PRN dosing for 24-48 hours. So once the subject had started dosing the expectation was to have all data entered into the EDC with 3 days from when subject ended treatment.

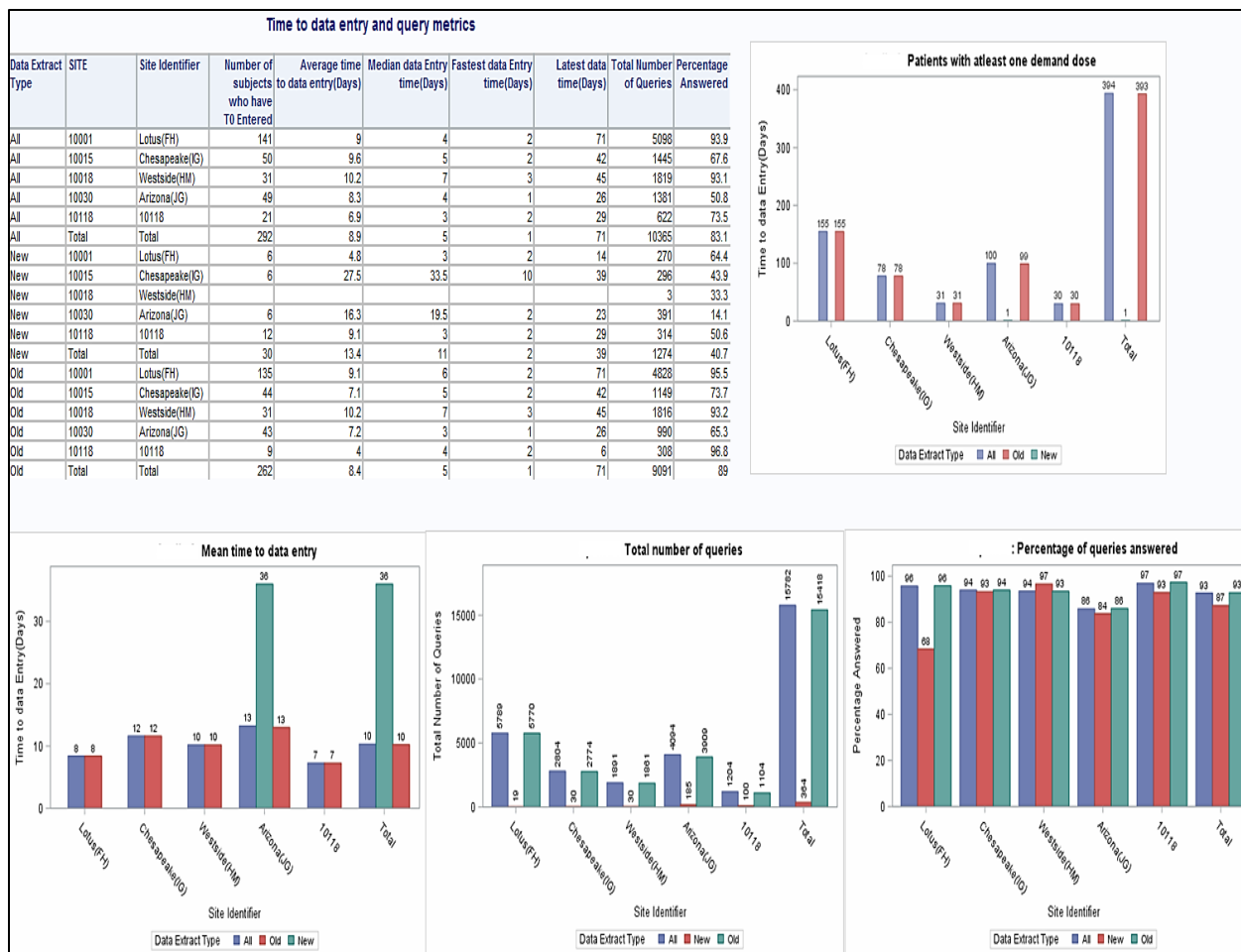


Figure 1: Timely Data Entry

Figure 1 shows example metrics that can be generated to show the pace of timely data entry.

- Metrics are show by site to access how fast or how slow each site is entering data.
- Table show metrics associated with data entry from the time a subject was dosed to the time data was entered into the database.
- The anchor for time to entry can be changed based on any of the 3 criteria mentioned above in this section.
- The entry times presented are grouped as
 - Overall – All data entered in the Database.
 - New – New Data entered since the last extract.
 - Old – Data existing in the database prior to the current extract.
- Other plots present the query and resolution metrics.
- Outputs were generated every week.
- Adjustments and updates were made to SAS macros as need based on feedback from study team.

```

ODS MSOFFICE2K file="G:\clinical\Data Quality Oversight\Reports\Apollo_study_metrics_&anchor_&subset.&date..xls"
gpath="G:\clinical\Data Quality Oversight\Reports" style=htmlblue
options( EMBEDDED_TITLES='yes' SHEET_INTERVAL='none' SHEET_NAME='Metrics' WRAPTEXT='on');

ods graphics on / reset width=600px height=400px imagename= 'DataEntry_1' imagefmt=gif;

proc sgplot data=seed_1;
  title " Apollo 1: Patients with atleast one demand dose " ;
  vbar siteid / response=d stat=freq group=typ GROUPDISPLAY= CLUSTER datalabel transparency=0.2 barwidth=0.5 ;
  format d 3. siteid $site. ;;
run;

proc sgplot data=final_1_&anchor_&subset;
  title " Apollo 1: Mean time to data entry " ;
  /* panelby typ; */
  vbar siteid / response=d_mean stat=mean group=typ GROUPDISPLAY= CLUSTER datalabel;
  format d_mean 3. ;
run;

ods graphics off;

ods MSOFFICE2K close;

```

Figure 2: Code sample

Figure 2 show sample code to generate

- The outputs are created using SAS macros and ods excel.
- Proc SGplot to create simple vertical bar charts which can be easily understood by the study team
 - Plot for number dosed subjects
 - Plot for mean time to data entry

Customized programmatic edits checks

Every EDC system has built in edit checks that are added to the system as part of database build during study setup phase. These consist of edit checks which are based on the study data validation plan. Complex checks which look across different pages and adhoc checks are not easy to build due the steps involved in adding edit checks to the EDC system. In some instances there might be a need to avoid excessive number of edit checks as this might burden the system and make user entry of data very cumbersome.

As important as it is to create these edits outside EDC, it is equally important to create the outputs in a form which makes it very easy for the study team members to digest the information and act quickly. With this ease of use as one of primary considerations the customized edits checks work book has a lot of user friendly features such as

- A excel work book with multiple tabs for each edit which can be accessed from the TOC which is the first sheet in the workbook.
- Auto filters on all sheets which facilitates filtering of new data issues vs old reviewed issues etc.
- Direct hyperlink to the EDC system so that user can directly go to the data point in EDC and act on issuing a query or mark something as resolved for future runs.

EDC_LINK	SUBJID	EXTYPE	ST_TIM	EN_TIM	DOSE_TYPE	DOSE_DATETIM	EDC_AUDITCOMMENT
edclink	10001-051	Temporary	26JUL16:10:36	26JUL16:12:55	Demand Doses	26JUL16:12:54	Response to Query
edclink	10001-051	Temporary	26JUL16:23:55	27JUL16:02:15	Demand Doses	27JUL16:00:35	Response to Query
edclink	10001-051	Temporary	26JUL16:23:55	27JUL16:02:15	Demand Doses	27JUL16:02:14	Response to Query
edclink	10016-001	Temporary	09JUN16:01:03	09JUN16:01:50	Demand Doses	09JUN16:01:46	
edclink	10016-029	Temporary	27JUL16:10:30	27JUL16:12:10	Demand Doses	27JUL16:10:30	Response to Query
edclink	10016-060	Temporary	17AUG16:20:28	17AUG16:20:55	Demand Doses	17AUG16:20:54	Data Updated
edclink	10016-108	Temporary	05OCT16:14:22	05OCT16:14:55	Demand Doses	05OCT16:14:53	
edclink	10029-046	Temporary	09AUG16:06:09	09AUG16:06:38	Demand Doses	09AUG16:06:10	
edclink	10030-106	Temporary	04OCT16:12:49	04OCT16:15:41	Demand Doses	04OCT16:12:56	

Figure 3: Hyperlinked Edits check with TOC

Figure 3 shows example of custom edits workbook created using SAS macros

- Top part shows the TOC with a brief description of all edits that are part of the work book.
- This TOC is hyperlinked and each one will take the user to the appropriate sheet that has the edit in this multi sheet document.
- Bottom part shows actual edit in its own sheet.
- First column “edclink” which is clickable takes user directly to the appropriate data point in the EDC system (assuming the user has access and is logged into the associated study).
- Additional information such as queries issued, resolutions, new data points are also available to the user.
- This additional information helps focus on what is most important and not review data points that have already been looked at in the prior runs.

```
ods excel file="G:\clinical\Data Quality Oversight\Programmatic edit tracking\Apollo\study_programming_edit_checks\edc_extract.xlsx"
options(SHEET_INTERVAL='Proc' EMBEDDED_TITLES='yes' autofilter='yes' SHEET_NAME='Edit Check' CONTENTS='yes' );

*****
** Dosing interruptions
*****

data interup;
set raw300&study..ex;
if lowercase(exyn)='y' and extype ne '' and EDC_CURRENTFLAG=1;

    st_time=dhms(exstdat,0,0,EXstTIM);
    en_time=dhms(exendat,0,0,EXenTIM);
    dur_min=(en_time-st_time)/60; /*minutes*/
    dur_hr=round((en_time-st_time)/3600,0.1); /*Hours*/
format st_time en_time datetimel4. ;
if &study = 1 %then %do;
    EDC_link =HYPERLINK("https://express54.bioclinica.com/Express54/TrustedUsers/Navigation.aspx?SponsorID=297&StudyID=TR001&Fullpath="
    || strip(tranwrd(edc_path, "/", "%2F")) || "/" || "edclink" );
%send;
%else %do;
    EDC_link =HYPERLINK("https://express54.bioclinica.com/Express54/TrustedUsers/Navigation.aspx?SponsorID=297&StudyID=TR002&Fullpath="
    || strip(tranwrd(edc_path, "/", "%2F")) || "/" || "edclink" );
%send;
run;

ods excel close;
```

Figure 4: Sample Edit code with hyperlink to EDC

Figure 4 show sample code that generates edit checks workbook in figure 3

- Uses ods excel to create work book.
- Option SHEET_INTERVAL='proc' creates the individual sheets for each edit.
- Option EMBEDDED_TITLES='yes' displays a title with description of each edit.
- Option autofilter='yes' creates excel auto filter across all sheets.
- Option Contents='Yes' along with "ods proc label" creates the clickable TOC as the first sheet.
- EDC_link is created using excel function "=HYPERLINK".

Custom Graphical Patient Profiles

Visualization of data is very powerful; the user can easily and quickly glean information as compared to looking at the same data in a data table/listing format. The approach here was to create graphical displays that help with clinical review and look for safety signals in subjects who discontinue study treatment or any other criteria for a group of subjects that might come up in the study.

All events/measurements which are impacted by study drug use occur relative to when the study drug was administered. Taking this as basis a SAS macro was built to calculate the relative time from treatment start to any event/measure for all subjects at any time in the EDC system export. Now taking this data another macro creates the graphical displays with events/measure as required for each subject.

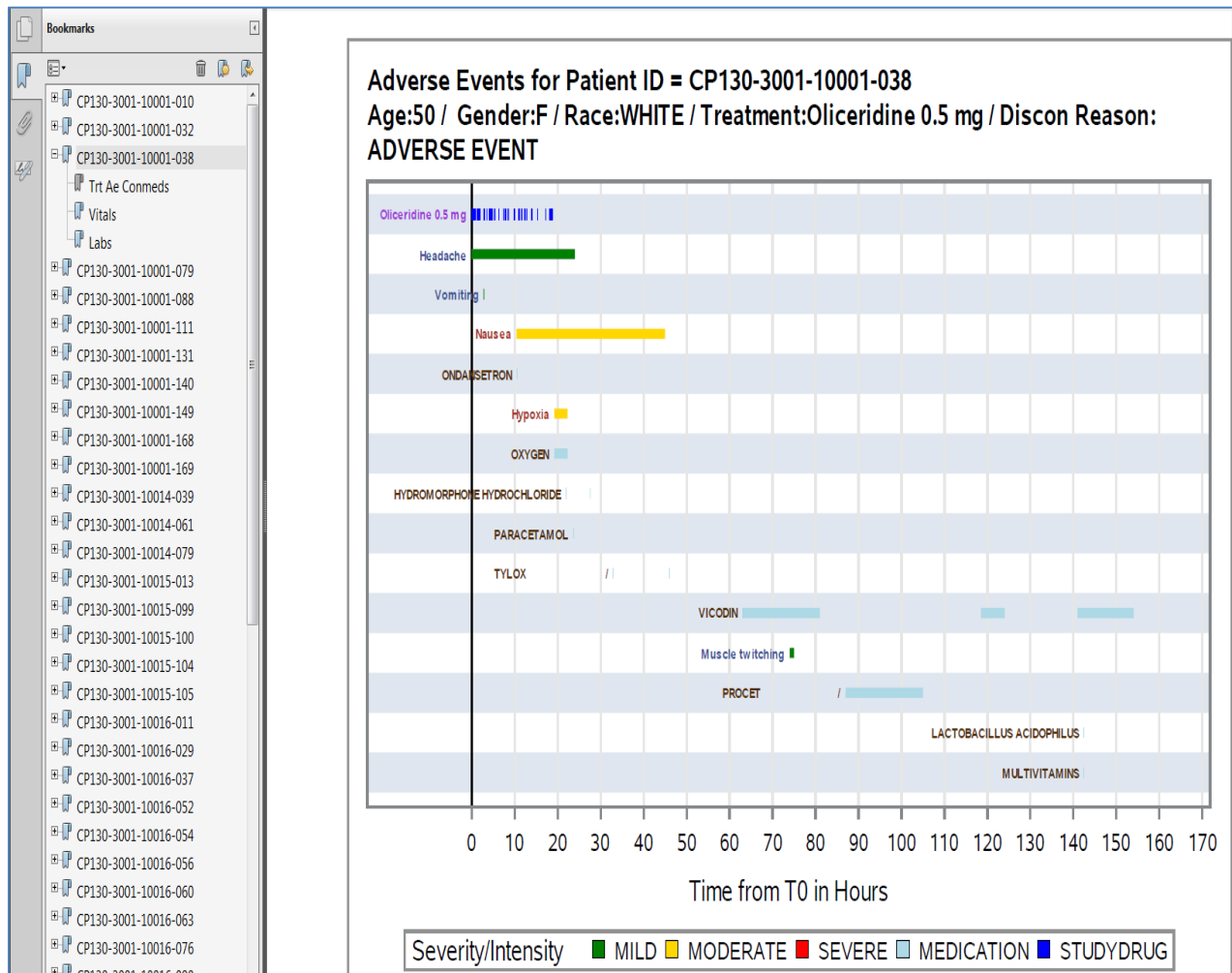


Figure 5: Graphical profiles

Figure 5 shows example graphical patient profile which is part of bookmarked pdf.

- Graphical profile of all subjects who discontinued study medications.
- The title provides information such as demographics, study treatment and reasons the subject discontinued study medication.
- X-axis show the relative time from dosing.
- Dosing PRN along with treatment is displayed on the top.
- Shows all adverse events for the subject with different colors for severity, in the example you can see there are 2 moderate adverse events.
- All Conmeds taken are also shown.
- Other important safety measure such as labs and vitals are also displayed in other graphs within the same document..

```
ods document name=pprofile_&i. (write);

ods proclabel="%cmpres(&spid&i.) ";
title j=1"Adverse Events for Patient ID = &spid&i. ";
title2 j=1 "stoprow." ;

proc sgplot data=temp datrmap=attrmap;

refline 0 / axis=x lineattrs=(color=black thickness=1) ;

highlow y=name low=stty high=stey / type=bar group=aesev
lineattrs=(color=black pattern=solid) attrid=Severity
barwidth=0.5 lowlabel=label highcap=hicap lowcap=lowcap nomissinggroup
labelattrs=(size=5 weight=bold) /*dataskin=matte */ fill /*fillattrs=(transparency=0.5) */ ;

keylegend / location=outside down=1 position=bottom opaque ;

xaxis grid label="Time from T0 in Hours" values=(0 to 170 by 10);

yaxis reverse display=(noticks novalues nolabel) colorbands=odd ;

run;
```

Figure 6: Sample code to generate profiles

Figure 6 show sample code to generate

- Saves the plots generated for each subject using ODS Document.
- Proc SGplot is used create the graphical profiles to display dosing, adverse events, Conmeds ,disposition events, labs, vitals

```
proc document name=pprofile_&i.;

/*loop through and copy the plots into this new dirrectory*/

make \pat_pid_&i.; /*create new directory*/
dir \pat_pid_&i.;
make \plots; /*create a plots directory with in this new dir, this will result in nested bookmarks when pdf is generated*/

dir ^^^; /*move to the top*/

%do j=1 %to %gcount;
setlabel &grph&j.. "%&lbl&j..";
move &grph&j.. to \Work.Pprofile_&i.\pat_pid_&i.\plots;
%end;

setlabel \pat_pid_&i. "%spid&i..";

quit;

ods pdf file="S:\TRV130\CP130-3001\programs\dev\tlf\output\Graphical_patient_profile_patients_who_discontinued_treatment.pdf" pdftoc=1 ;

%do i=1 %to %pidc;

proc document name=pprofile_&i.;
replay \pat_pid_&i. ;

%end;

run;
```

Figure 7: Sample code to created bookmarked profile PDF

Figure 7 show sample code to generate

- Proc document is used to re-arrange the plots generated.
- Bookmarks are created using ods proc label
- Using ods pdf the final document is programmatically generated with all hyperlinks in place.

CONCLUSION

The techniques available in SAS can be leveraged to develop a frame work of tools that are very user friendly and help with study conduct, monitoring, data cleaning and clinical data review. Once an initial setup is in place, cross functional input from clinical operations, pharmco vigilance, clinical development can be used to further develop and augment these tools and make them invaluable for a study team.

REFERENCES

Sanjay Matange (2013) "Patient Profile Graphs Using SAS" Paper 160- SGF

Darylene Hecht(2011) "PROC PRINT and ODS: Teaching an Old PROC New Tricks" Paper 270- SGF

CONTACT INFORMATION

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