INDEPENDENT DATA REVIEWS
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ABSTRACT
Clinical trials must be conducted with the highest standards of quality to ensure that the research question is answered in a reliable, valid and unbiased manner. For certain double-blinded clinical trials, efficacy and safety may require monitoring by Data Review Board (DRB) and Data Monitoring Committee (DMC). This is to ensure patients receive the proper level of care. The treatment assignment must remain blind for patient results and their treatment assignments, so that internal decision makers and reviewers can make independent, unbiased decisions related to the study. So how do we proceed? This paper discusses how Gilead Sciences, Inc (GSI) performs DRB and DMC independent reviews in a cost saving, flexible, and efficient way.

INTRODUCTION
Some clinical trials can be multi-center and can have multiple investigators. Some investigators can be liberal and some investigators can be conservative in their standard of care. The idea behind independent data reviews is to re-evaluate the data by central boards like Data Review Board (DRB) and Data Monitoring Committee (DMC), such that all cases will be reviewed in a blinded fashion with respect to treatment group and provide their feedback to the sponsor (GSI).

During a double-blind clinical trial a Contract Research Organization (CRO) generates the Tables, Figures, and Listings (TFLs) for the sponsor, so that the sponsor remains completely blinded. But the problems with this approach are that: the cost is high, unpredictable quality, which means poor outputs, and inflexibility in terms of output customization.

At GSI, our processes in handling DRBs and DMCs are the same. For each DRB or DMC, we generate TFLs in-house using dummy treatment codes. Once the outputs are complete and validated, we transfer the TFL creation programs to the CRO who has access to the actual treatment codes. At this point, the CRO will be able to rerun the outputs with respect to the actual codes and deliver the unblinded results to DMC or DRB. In this approach, the CRO has minimum involvement, reducing outsourcing cost, and we also have a better control in terms of the quality of the outputs. For those programs developed in house, they are easy to maintain across multiple studies and customize which also give us more flexibility.

Figure 1 describes the process in a flow chart.

Figure 1: Process Flow Chart

- Create TFL programs with dummy treatment codes
- Transfer Programs to CRO
- Rerun TFL programs with real treatment codes
- Real treatment code
- Unblinded analysis outputs
GENERAL CONSIDERATION

We at GSI, use proprietary macros, a common directory structure, and programs running using proprietary shell scripts that establish the standard execution environment. Our standard computing environment is SAS™ 8.2, running on Unix. We do not control the target environment at CRO, which is probably very different. Before we transfer the programs to the CRO, we should also consider that if the target has the same operating system, and/or if the target uses the same version of SAS that some of internally developed macros will not run on the target’s version of SAS. Often the CRO environment is Windows. Therefore, we must first create portable version of the programs and test them before transferring them to the CRO. The following steps demonstrate how to create portable version of programs.

STEPS TO CREATE PORTABLE VERSIONS OF PROGRAMS:

Once the TFLs have been generated and validated in the production directory then,

1) Set up a simplified directory structure on Windows for the files to be sent to the CRO.

It consists of:

root directory/
   subdir1/
   subdir2/
   subdir3/
   subdir4/

2) Copy the raw datasets from the production directory to the appropriate directory created in Step 1.

3) Compile the macros for the analyses and save them to a catalog. To do this,

   a) Copy the SAS macros that are used for the analyses
   b) Prepare each macro for compiling and storage. The only requirement is that the macros have the /store option added to the %macro statement. For example,

      %macro xyz( );
      this becomes %macro xyz( ) / store;

   c) If we want to hide the source code in the macros, add the following statements to the top of each macro (after the %macro statement):

      options nomprint;
      options nosymbolgen nomacrogen nomlogic;
      %let debug=*;
      (This is an internal macro variable. This variable combined with above options hided the source code)

4) Create a Windows format catalog. To do this,

   Write a program that creates the format catalog in the local directory. The LIBNAME and PROC FORMAT statements should look like this:

   libname library = "." ;

   Proc format library = library ;

5) Copy SAS programs used to create the analysis datasets and the TFLs to the appropriate directory created in Step 1.

6) Create a program whose job is to properly initialize the SAS environment for the programs copied in Step 6. It must set the global macro variables that are normally set by out standard initialization files and established by the program execution scripts in Unix.
7) Create a Windows batch file that will run all the SAS programs that we send in the correct order. The analysis file creation programs must execute in a specific order and execute before any TFL programs.

Example:  
%sas% -sysin a_ademog
%sas% -sysin a_albcnvs
%sas% -sysin t_random

8) Create a password protected WinZip archive of the entire structure.

9) Run a test extraction of the files in the WinZip archive. Extract the files to a new location so that testing will not overwrite any of the original files.

10) Test run the programs

11) Evaluate the results of the execution by comparing the new outputs against the original outputs created on Unix.

12) Send the password protected WinZip archive to the CRO via email. Phone the contact person and tell them the password.

13) Let the project statistician, lead programmer know that the programs have been sent.

14) The CRO will extract the files, apply the real treatment codes, run the programs and transfer to the appropriate DRB or DMC.

CONCLUSION
This process not only provides a cost saving advantage, it also minimizes the time waiting for CRO to generate unblinded outputs. Since the programs are developed in-house, and used across various studies, we can also ensure consistency across each of the DRB and DMC review. Further, with all programming development performed in house, we can also monitor data more closely and resolve any data issues more quickly, without delaying the process of getting accurate and clean unblinded outputs to DRB or DMC for review. In this approach GSI also has more control in all aspects of the study.

CONTACT INFORMATION
Your comments and questions are valued and welcomed.

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