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Automated Solution Drives Efficient Progress of DMC Analysis Projects

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ABSTRACT

In clinical trials, the Data Monitoring Committee (DMC) is responsible for reviewing the safety or efficacy of data under unblinded manner during the trial. The project statistician should assist the Independent Statistical Team (IST) in preparing programs and generating closed-door meeting report templates based on the pre-specified interim analysis plan using the dummy arm codes. The IST uses codes that distinguish study arms to conduct the analysis and generate results. This article describes an efficient automated solution that generates all necessary TFLs with just a click of a batch file (.bat), which is able to protect the company's intellectual property, reduce the workload of the independent statistical team, ensure the accuracy of results, and accelerate the project timeline. By providing the efficient and accurate automated solution, we greatly improve data transparency, accuracy, and review efficiency, data transparency and accuracy, aiding the DMC in expediting review and decision-making processes, thereby improving the overall progress and quality of clinical trials.

INTRODUCTION

DMCs can be traced back to 1967 and the 'Greenberg Report', and in 1979 the National Institutes of Health (NIH) in the USA issued a policy that 'every clinical trial should have prevision for data and safety monitoring'. In the 1990s, the US Food and Drug Administration (FDA) reviewed operational aspects of safety monitoring in clinical trials, the NIH further developed a policy on data and safety monitoring committees, and guidance documents by the International Conference on Harmonisation (ICH) also included references to DMCs.

DMCs were initially used in large randomised multicentre clinical trials to allow for interim safety monitoring of study data to ensure the ongoing safety of trial participants. More recently, DMCs have been increasingly used in industry sponsored trials, from phase I to III.

The use and role of DMCs has evolved over the past decades. In 1990, only 10% of trials published in medical journals reported using DMCs compared with 25% in 2000. A report of an analysis of the ClinicalTrials.gov database in 2010 of trials involving indications such as cardiovascular disease, oncology and mental health, showed that 41% of registered trials reported using a DMC.

Clinical trials frequently extend over a long period of time. Thus, for ethical reasons it is desirable to ensure that for patients participating in such trials there is no unavoidable increased risk for harm. On the other hand it is also important to ensure that a trial continues for an adequate period of time and is not stopped too early to answer its scientific questions. An independent Data Monitoring Committee (DMC) as a group of experts external to a study that reviews accumulating data from an ongoing clinical trial might serve such tasks. While in general safety monitoring should be the major task for a DMC, other aspects of a clinical trial (e.g. study integrity, design aspects) might also be assessed by a DMC. When monitoring a clinical trial a DMC might have to review accumulating data from an ongoing clinical trial in an unblinded fashion. Based on these reviews, a DMC has the capacity to make recommendations that might impact the future conduct of the trial. As access to unblinded treatment information during a clinical trial has the potential to introduce bias to future trial results, the impact of human factors on the results should be minimized in order to ensure the scientific integrity of a clinical trial involving a DMC.

In the last two decades, various health authorities have issued guidance documents on the use of DMCs in clinical trials. The FDA issued a finalised guidance document in 2006 on 'Guidance for Clinical Trial Sponsors, Establishment and Operation of Clinical Trial DMCs'. The European Medicines Agency (EMA) issued a 'Guideline on DMC' that was adopted by the Committee for Medicinal Products for Human Use (CHMP) in July 2005 and the guidelines came into effect in January 2006. In China, the National Medical Products Administration (NMPA) issued the 'Guideline on Clinical Trial Data Monitoring Committees (for Trial Implementation)' in 2020. These official documents highlight the importance of independent data monitoring and the regulatory relevance of the composition and functioning of DMCs.

In this context, accurately and efficiently generating unblinded results is indispensable for the DMC as well as for the smooth progress of the entire clinical trial.

KEY STEPS IN CREATING AUTOMATED PACKAGE

IDENTIFYING DATA REQUIREMENTS

Communicate with the Data Management (DM) team to understand the data transfer types and formats. This step ensures we have all the necessary information to process and analyze the data correctly.

WRITING TEST PROGRAMS

Generate dummy data sets based on randomization code. Then, write the corresponding blinded programs to produce the dummy reports according to the study protocol and statistical analysis plan (SAP).

QUALITY CONTROL AND VALIDATION

After the programs are written, we conduct rigorous quality control and validation processes. Internal reviews and simulated tests ensure the programs run correctly and produce accurate results.

MACRO PROGRAM STORE

Place the validated test program into the unblinded folder. Use tools to batch store company and individual macro programs, modify some options in the program header.

GENERATING BATCH FILES

Based on the dependencies between programs, generate a batch file that follows the correct execution order. This batch file undergoes multiple rounds of review and testing to ensure it generates accurate results.

PROVIDING PROGRAMS AND SUPPORT

After mock testing, the package, along with the corresponding documentation, are delivered to IST. We also provide technical support to help them understand how to use the programs and resolve any issues that may arise.

MACRO PROGRAM STORE

COMPILING AND STORING A MACRO DEFINITION

To compile a macro definition in a permanent catalog, you must first create the source for each stored compiled macro. To store the compiled macro, use the following steps:

1. Use the STORE option in the %MACRO statement. You can use the SOURCE option to store the source code with the compiled code. In addition, you can assign a descriptive title for the macro entry in the SAS catalog, by specifying the DES= option. For example, the %MACRO statement in the following definition shows the STORE, SOURCE, and DES= options:

```
%macro myfiles / store source
     des='Define filenames';
  filename file1 'external-file-1';
  filename file2 'external-file-2';
 %mend;
```

2. Set the MSTORED system option to enable the stored compiled macro facility. For more information, see MSTORED Macro System Option.

3. Assign the SASMSTORE option to specify the SAS library that contains or will contain the catalog of stored compiled SAS macros. For example, to store or call compiled macros in a SAS catalog named MyLib.SASMacr, submit these statements:

```
libname mylib 'SAS-library';
options mstored sasmstore=mylib;
```

For more information, see SASMSTORE= Macro System Option.

4. Submit the source for each macro that you want to compile and permanently store.

You cannot move a stored compiled macro to another operating system or to a different release of SAS. However, you can move the macro source code to another operating system or to a different SAS release where you can then compile and store it. For more information, see your host companion.

CALLING A STORED COMPILED MACRO

Once you have set the required system options, calling a stored compiled macro is just like calling session compiled macros. However, it is important that you understand how the macro processor locates a macro. When you call a macro, the macro processor searches for the macro name using this sequence:

1. the macros compiled during the current session
2. the stored compiled macros in the SASMacr catalog in the specified library (if options MSTORED and SASMSTORE= are in effect)
3. each autocall library specified in the SASAUTOS option (if options SASAUTOS= and MAUTOSOURCE are in effect)
4. the stored compiled macros in the SASMacr catalog in the SASHelp library

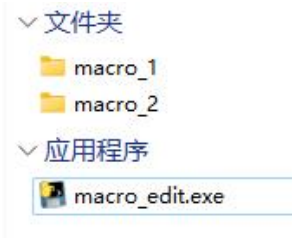
You can display the entries in a catalog containing compiled macros. For more information, see Macro Facility Error Messages and Debugging.

BATCH MODIFYING MACRO PROGRAMS WITH PYTHON

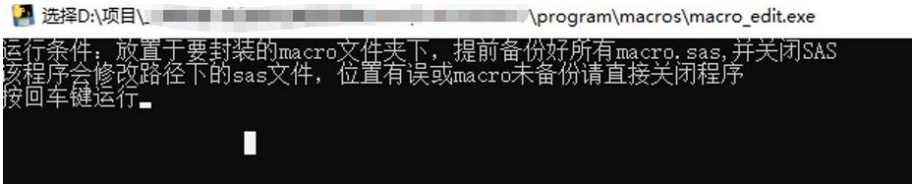
Based on the keyword %macro, insert "/store" at the specified position. Additionally, you can add time information to control the validity period of the stored macro. The tool will also generate a SAS program to run SASMSTORE and create some documentation files.

```
result = split('%macro', text, flags=I)
part_01 = result[0]
result = result[1:]
part_02 = "\n%macro".join(result)
result = part_02.split(';')
  if search(r"\).*/", result[0]):
    result[0] = result[0] + ' store;'
  else:
    result[0] = result[0] + '/store;'
result[0] = result[0].format(creat_time=creat_time)
part_02 = ";".join(result)
prat_02 = sub('%mend',  part_02, flags=I)
```

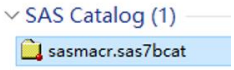
1. Place the program in the path where the macro to be encapsulated is located.



2. Double-click to run it and enter this interface then follow the program prompts and press Enter as needed.



3. Use SAS to run the generated SAS program to complete the encapsulation of the macro program, create the macro package.



Of course, you can also use tools other than Python to achieve this effect.

ADVANTAGES

AUTOMATED EXECUTION

Our Automated Solution is designed to automatically generate all necessary TFLs with just a click of a batch file (.bat). This greatly simplifies the workflow for the IST.

INTELLECTUAL PROPERTY PROTECTION

The macro programs are stored, protecting intellectual property while ensuring stability and reliability.

ERROR REDUCTION

The IST does not need to modify the code, reducing the possibility of human errors and ensuring the correctness of the results.

INCREASED EFFICIENCY

The automated unblinded programs significantly reduce the workload of the IST, speeding up the production of unblinded results and thus accelerating the project timeline.

CONCLUSION

In clinical research, creating and providing unblinded results is a crucial step to ensuring data transparency, accuracy, and review efficiency. Through rigorous program design and quality control, we can provide an efficient and accurate automated solution to IST, aiding the DMC in expediting review and decision-making processes, thereby improving the overall progress and quality of clinical trials.

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11. SAS Help and Documentation.

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