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The Role of the Blinded Programmer in Preparation of Data Monitoring Committee Packages (for Clinical Trials)

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ABSTRACT

A data monitoring committee (DMC) is a group representing clinicians and biostatisticians having expertise in clinical trials and are appointed by study sponsors to provide an independent assessment of the safety, scientific validity, and integrity of clinical trials. In the United States, the FDA requires the sponsors to establish a DMC in all clinical trials that assess new treatment interventions. The FDA also strongly recommends establishing a DMC in clinical studies which have double blinded treatment assignment, have substantial safety concern, or have a significant impact on clinical practice.

Blinding in clinical trials is a procedure in which one or more personnel are unaware of which treatment participants are receiving, a technique that maintains the ethics and integrity in a study and reduces the bias in design or execution of the trial and its results. A Blinded programmer will use the blinded data and dummy treatment to produce analysis level datasets and clinical reports in support of DMC package. Another unblinded programmer will use these analysis programs on unblinded data and actual treatment to produce analysis level datasets and clinical reports for DMC review. The Blinded programmer plays a key role in developing and maintaining of all analysis programs and maintains communication with unblinded programmer. This paper will walk through the role of blinded programmer in preparation of DMC package and critical communication with unblinded programmer when unblinding happens to resolve any challenges and issues.

INTRODUCTION

This paper will provide a comprehensive overview of the role of the blinded programmer in the preparation of DMC package, focusing on their communication with the unblinding team, to better understand challenges faced working on blinded data and resolution for producing high quality deliverables. It will describe in depth the workflow to prepare a high-quality DMC package, challenges faced by blinded programmer and an overview of the timelines for the steps to successfully prepare DMC package. It will also highlight how to establish clear and transparent communication with unblinding team.

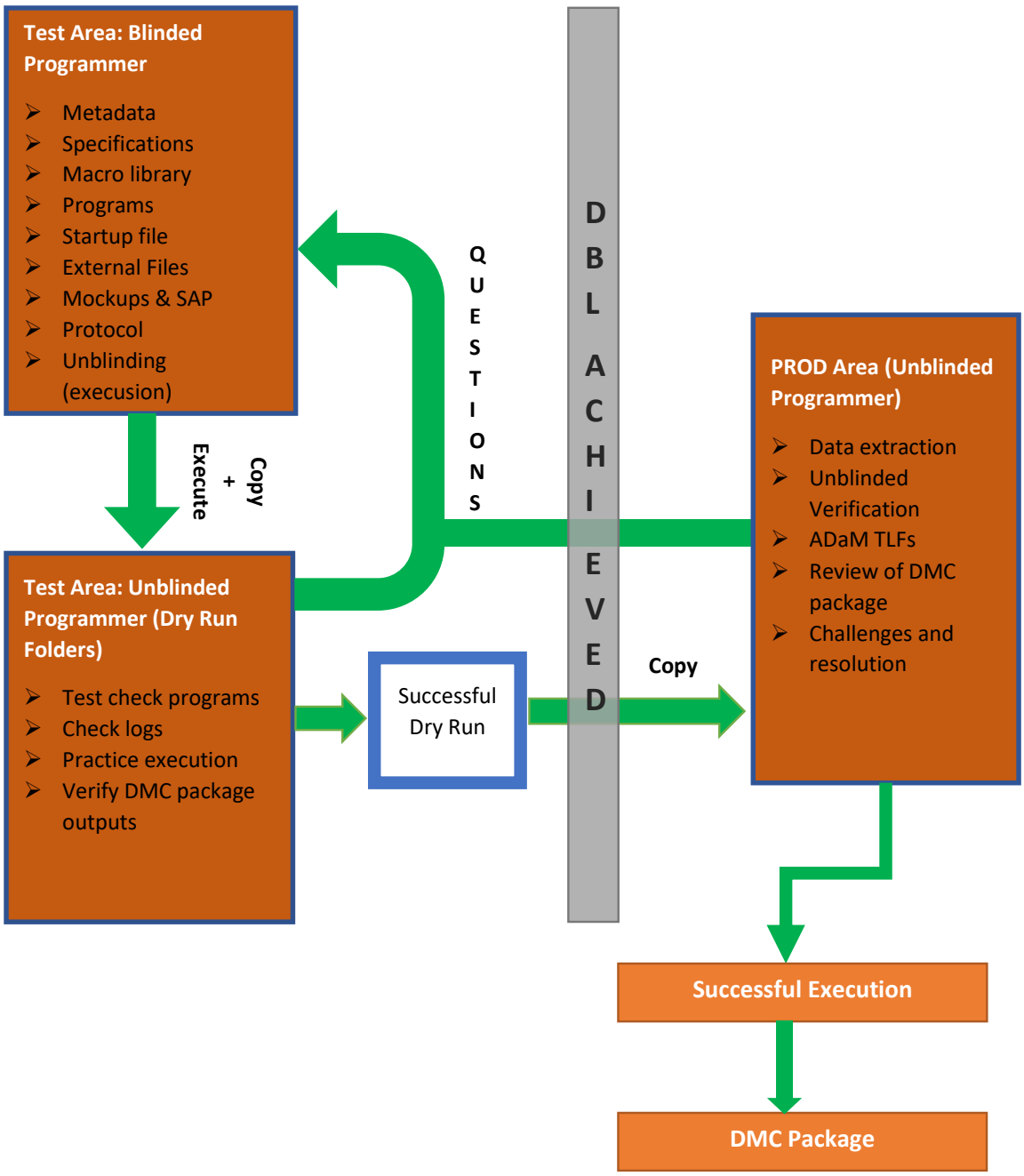

Figure 1. Overview of Activities

PREPARATION OF DMC PACKAGE IN TEST AREA:

The programmer should review Protocol, CRF (Case Report Form) and sSAP (Supplemental Statistical Analysis Plan) before starting any of the DMC related activities to get familiar with the study. The steps below are recommended for preparation for a successful dry run.

1. **Data Extraction:**
   The programmer should work with the statistician to set up study folders beforehand, at least 3 to 4 months before the Database Lock date, to prepare for the DMC package. The programmer should work with the statistician to create the data extraction schedule, obtain necessary blinded data extraction permission, and collaborate with the clinical database team before data extraction. After each data extraction, the programmer should review for any unwanted errors or warnings from data extraction log and communicate the issues with clinical data base team.

2. **Metadata & SDTM data quality check:**
   The programmer should review and implement any internal metadata derivation rules like lab toxicity grade derivation, normal ranges for lab tests results and normal range unit conversions, derivation of visit window derivation etc. The programmer should apply the analysis cut-off date to all the SDTM data and keep the uncut SDTM data in separate folder for any analysis questions that arise which may require reviewing the uncut data. The programmer should assign the dummy treatments to all necessary SDTM data.

   The programmer should also check the quality of the SDTM data and adherence to CDISC standards with the help of Pinnacle 21 tool. The issues found should be communicated with the wider team and ensure they get resolved in time.

3. **Review of ADaM specifications & TLF mockups:**
   The programmer should check all the variables needed to create TLFs are included in ADaM specifications and derivation of these variables such as treatment related variables, population flag variables, baseline variables, exposure related variables etc., are in line with the SDTM data. The programmer should work with the statistician to update the derivation of these variables where it is necessary to align with the SDTM data.

   The programmer should review TLF mockups for their consistency of titles, footnotes, sub-setting conditions and any other necessary information needed to create high quality TLFs. The programmer should also verify the TLF mockups are align with the ADaM specifications.

4. **Analysis & Reporting activities:**
   After receiving the SDTM data and applying all the internal metadata rules, the programmer can start working on the development of ADaM datasets and their validation. The programmer should examine the ADaM datasets with the help of the Pinnacle 21 tool and resolve the issues to improve the quality of the ADaM datasets. Simultaneously, programmer can start working on development and validation of TLFs and collaborate with statistician to review all the ADaM datasets and TLFs.

PREPARATION OF EXECUTION INSTRUCTION DOCUMENT:

The programmer should prepare execution instruction document for the unblinded programmer to succefully create a DMC package. It should have clear step-by-step instructions about which documents, metadata, macros, programs etc., should be copied from TEST (Blinded data) folders to respective PROD (Unblinded data) folders.

This document should outline instructions to update the set-up programs for successful execution in PROD area i.e., startup programs, data extraction macro, etc. The guidance may include the update in working environment (TEST vs PROD), data base lock staging number, recipient email (unblinded programmer & statistician) for data extraction notification, etc.

This document should include instructions to verify unblinded treatment allocation. The programmer should provide a guidance document which has all the instructions on how to perform verification of the unblinded treatment allocation assignments to subjects/patients.

The programmer should provide the sequence in which ADaM programs should be run and include snapshot of all the expected and known warnings and/or notes from the ADaM and TLFs logfiles in the execution instruction document, which are acceptable and do not have impact to any of the analysis.

This document should also list all the unblinded team members contact details i.e., unblinded statistician, unblinded data management team personal, unblinded clinical scientist etc., along with details of technical persons involved in clinical data base maintenance repository.

PRACTICE DRY RUN IN TEST FOLDERS:

The programmer should create separate dry run TEST folders in advance, at least 3 to 4 weeks of the DBL, and provide access to the unblinded programmer. The programmer should copy all the documents, metadata, programs, execution instruction document, specifications, and mockup of TLFs included in the DMC package.

The unblinded programmer should review the execution instructions provided by the blinded programmer and verify all the necessary documents, programs and metadata are available to perform a practice dry run. After review of execution instructions, the unblinded programmer should follow the step-by-step instructions and practice-run producing all the ADaM datasets and TLF programs and review all the logs and outputs. The unblinded programmer should reach out to blinded programmer for any question or concern arise while executing the programs and for any issue seen in the logs or outputs which is not mentioned in execution instruction document.

Practicing the dry run in a TEST folder, before the database lock, helps the unblinded programmer to familiarize themselves with the working environment, folder structure, statistical computing platform, execution of workflow, and clinical reports required for DMC package, etc. This is the best time for unblinded programmer to collaborate with the blinded programmer to iron out any outstanding issues related with the dry run.

PREPARATION OF DMC PACKAGE IN PROD AREA:

After successfully completing the dry run, the unblinded programmer should copy all the latest documents, metadata, programs, specifications, and mockups from practice TEST dry run folders to PROD folders as per execution instruction document.

The unblinded programmer should begin data extraction on the planned database lock date once data base staging has been completed. The unblinded programmer should verify the data extraction program for production related changes mentioned in the execution instruction document. After the successful data extraction, the unblinded programmer can notify the study team about completion of this step.

Once data has been extracted successfully, the unblinded programmer should verify the assigned treatment as per the unblinded treatment allocation. The unblinded programmer should work with the unblinded statistician to verify the correctness of the treatment assignment before embarking on next tasks.

After successful verification of treatment assignment, the unblinded programmer should apply any data enrichment steps such as application of the cut-off date on SDTM data and run the ADaM programs in sequence as per execution instructions. After completion of the ADaM programs run, the unblinded programmer should check issue log and ensure no new warnings and/or notes are observed compared to what has been documented in the execution instruction document.

Once ADaM datasets have been generated and quality verified, the unblinded programmer should run all the TLFs as per the execution instruction document and check for any unwanted errors and/or warnings. The unblinded programmer should pay close attention to the execution instruction document for any tables to be generated with the total column. The unblinded programmer shall combine all these TLFs into one document as DMC package, for ease of statistical review and to compare with the blinded TLFs.

CHALLENGES AND RESOLUTION:

1. **Data extraction failure:** It is expected to have successful data extraction from clinical data base repository but in rare cases, it may fail. In this scenario, the unblinded programmer should communicate with the blinded team and follow up with the technical person involved in clinical data base maintenance repository mentioned in the execution instruction document.

2. **Unblinded Treatment verification:** This process cross verifies unblinded treatment allocation with unblinded demographic (DM) and exposure (EX) domains. This process will help determine accuracy of treatment arms and exposure data are consistent with allocation schedule and it will help verification of all the randomized subjects. Any deviation should be reported to unblinded study team and discuss the path forward.

3. **Exposure Dataset:** The unblinded programmer should pay close attention to SDTM exposure dataset to ensure that all treatment and dose related variables are unblinded properly. For any inconsistency in exposure dataset, the unblinded programmer should reach out to unblinded study team for their attention and guidance.

   The unblinded programmer should carefully review exposure ADaM program to ensure treatment names (EXTRT) used are correct and are the same as exposure domain in order to run successfully. Any deviation or mismatch in treatment names (EXTRT) in the ADaM program should be communicated with blinded programmer for correction without compromising unblinding of the data.

   The blinded programmer has worked on dummy data and hence some of the issues related with the dosing interval or dosing strength may go unnoticed in blinded data so the unblinded programmer needs to pay close attention to dosing related variables in the exposure ADaM program.

4. **TLF Review:** The unblinded team should review carefully the unblinded TLF package and compare it with blinded TLF package to ensure quality and correctness of TLF package. The total column comparison between the DMC package and blinded TLFs will serve as one of the quality assurance parameters for the unblinded team. The mismatch of total column should trigger a more detailed review of the table and discussion with the blinded team. Since unblinded exposure tables cannot match blinded exposure tables, the unblinded team should ensure careful independent review of these tables.

5. **The Protection of the Blind:** Establish clear communication protocols within the execution instruction document to ensure that all blinded and unblinded members understand their role and the importance of maintaining the blind and protection of the unblinded data. As the DMC occurs while study is ongoing, any inadvertent unblinding can compromise the integrity of the study.

   The unblinded programmer should ensure that all communication that happens post database lock with the blinded team i.e., any data issue or programming logic should not carry data with treatment information. The communication through email, chat or screensharing must be done carefully to avoid accidental exposure of treatment information with the blinded team.

CONCLUSION:

A comprehensive data monitoring committee (DMC) package is essential for ensuring the reliability and validity of the data collected in clinical trials. The blinded programmer plays a crucial role by preparing and maintaining the specifications, metadata, and programs for the DMC package. The blinded programmer also prepares clear execution instruction document for the unblinded programmer to successfully work on unblinded data and prepare quality DMC package. The protection of the blind in clinical trial is utmost important and setting up clear communication with the unblinded team upholds the ethics and integrity of the overall clinical trial.

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