

Effective Statistical Programming Preparation and Support for CFDA Self-Inspections and Onsite Inspections

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ABSTRACT

On July 22, 2015, the CFDA requested that all clinical studies for registration purposes in China be audited by CFDI (Center for Food and Drug Inspection, CFDA) during the NDA/sNDA process prior to obtaining the imported drug license. CFDI will ask sponsors to conduct self-inspections in advance and arrange formal on-site inspections to the clinical trials sites or central laboratory subsequently depending on the technical review progress of the NDA/sNDA application by CDE (Center for Drug Evaluation, CFDA). The purpose is to ensure the integrity and quality of the clinical trials and to confirm the associated data reliability or trustworthiness. Statistical Programming teams need to collaborate with other functions (e.g. Statistician, Data Management, Clinical scientist, CRA) to prepare for and support the inspections. The Statistical Programming team plays a critical role in this activity because we are familiar with the clinical trial data, which is the starting point for analysis supporting CSR, and we know the traceability from data collection to accurate data package we submit to the agency. This Paper will introduce the normal process, best practices, and common issues during these inspections, from a statistical programming understanding and perspective.

INTRODUCTION

China's recent drug regulatory reform has emphasized that clinical trial data must be authentic and reliable. The self-inspection and on-site inspection conducted by CFDI are the measures to raise drug quality during the CDE technical review.

Self-inspection:

- Companies will prepare and submit a self-inspection report, together with copies of clinical trial agreements, introduction of key investigators and other supporting documents. Companies may also voluntarily withdraw their registration applications from CFDA by the same deadline in case they have identified any inauthentic, incomplete or other non-compliant trial data through self-inspection.

On-site Inspection:

- CFDI will notify the sponsor one week before the on-site inspection. Usually CFDI will issue the circular on the 3rd week of each month on what documents and requirement for the on-site inspection.
- The on-site inspection will take around 1 week, depends on the study complication, site location, etc. For each site, there will be a kick-off meeting to introduce the process and scope, and closing meeting to finalize the findings of each site. There will be a final meeting on the last day of the last site to close the whole inspection.
- Sponsor will submit the formal response and explanations regarding of issues and findings within one week to CFDI after the inspection.
- CFDI/CDE will hold experts meeting internally to discuss the findings and response received.
- CFDI will hold communication meeting including the sponsor and site representative. If the sponsor accepts the inspection report then submission will be transferred to CDE. CDE will evaluate both the technical review report and inspection report to decide on whether to approve the application.

The inspection work is a joint effort by a cross function team, including clinical scientist, clinical operation, and submission teams. This paper will typically focus on the topics and process requiring statistical programming involvement.

SELF-INSPECTION:

The self-inspection mainly focuses on the below priority areas related to data analysis and reporting:

- Whether the locked database is consistent with the original data, whether the data used in statistical analyses and summary reports are consistent with the original records and database, and whether there are changes in data, and the explanations for such change.
- Screening, inclusion and exclusion of subjects in clinical trial institutions, compliance with the inclusion and exclusion criteria and review of subjects participation criteria.
- Data with respect to the number of clinical trial protocol deviations inclusion and exclusion.
- Reporting of adverse events.

There are 2 self-inspection forms (Phase III and PK) that need to be filled and submitted according the study type. The forms will be referred prior to and during the on-site inspection and help inspectors set up their inspection plans, e.g. select risk sites, plan inspection schedule across multiple cities.

There are a few sections are mandatory to fill related to statistical analysis, e.g. basic information on the person and organization which performed statistical analysis. Also we need to fill out the inspection form with number of subjects by site:

- Plan to enroll
- Screened
- Randomized
- Completed
- PD/AE/SAE

We need to cross check with database, CSR, SAR together with the numbers from site to make sure the number is consistent across the multiple sources. If anything not inconsistent, we should better provide statement documents as explanation, e.g. How to define completers in the protocol; What is the difference between PD/PV and impact the analysis; How is AE cases counted, etc.

ON-SITE INSPECTION

There are some areas related to analysis included in the inspection purposes and key points:

- Check the consistency between the original data, statistical analysis and summary report and the locked database.
- Check whether the database is modified after locking and whether there is modification explanation; verify and record data that have been arbitrarily revised without explanation.
- The number of enrolled and completed cases in the locked database shall be consistent with the number of actually enrolled and completed cases; verify and record the number of inconsistent cases.
- Check the consistency between the locked database and the primary efficacy indicators and safety indicators recorded in the CRF and original medical records (if there are revisions, further check the question form's revision records); record the number of examined cases and data that have been arbitrarily revised.
- Check the consistency between the number of cases in the statistical report and the locked database.

PREPARATION BEFORE THE ON-SITE INSPECTION

Good preparation is the most important step at the beginning. This helps the whole study team to monitor the inspection readiness and preparation status. Typically this enables team to setup workable and reasonable timelines, to make progress as planned, and to adjust plan and delivery.

For most studies conducted in-house, there would be relative ease because we were familiar with the analysis process and understand the data package. For those outsourced studies not developed by the internal team and platform, we need to make sure the datasets, TLF package, programs retrieved from external partners are complete and can be used in the internal programming environment.

The comprehensive studies documents should be collected in a central location to enable reference and cross checking quickly, including protocol, CSR (with full Appendix), sub-center's summary table, SAR, DBL memo (with DBL date and data unblinding for analysis date) and final self-inspection forms. If Chinese version documents are available, please pay attention if any translation mistake among them.

The following analysis and table/listing generation should be prepared in advance:

- Repeat CSR Analysis to get familiar with the data, repeat the analysis dataset and TLF used to supporting CSR, create index file for quick search analysis content and source direction.
- Create site-level data listing to guide clinical and operation team to cross check with site reporting
 - Subjects screened and reason for subjects who did not meet eligibility requirements
 - Treatment assignment
 - Subjections discontinuation
 - AE/SAE/Death (may need to translate the terms to Chinese)
 - PD/PV
 - Demography
 - Subject accounting (population set)
 - Concomitant medication and prior medication
 - Medical history
 - Protocol specific safety endpoints
 - Efficacy endpoints (including the raw value if the endpoints are derived)
- Create a centralized excel file including the site level summary, e.g. numbers of subjects enroll, randomized, treated, discontinued, completed.
- Cross check the AE/SAE numbers, population numbers, PD numbers between the self-inspection form and dataset/CSR tables.
- Understand the PD (or/and PV) analysis, e.g. source data, derivation, related PP population.
- Familiar with CRF form associated submitted data.
- Understand missing data imputation handling methods.
- Conduct outlier analysis if applicable.

SUPPORT DURING THE ON-SITE INSPECTION

Statistical programmers can get access the datasets using SAS environment (e.g. SAS datasets in the platform or xpt files submitted in CD). On-site support is quite important to assist the inspector to get familiar with the data and extract the information they need. The key points are different in inspection areas separately, for example, clinical sites, central labs, and PK.

Clinical Site

The Clinical Site is the main area for the inspections. Normally there will be following cases needing programmer support and input.

- Assisting the inspectors to read the data disk (or archived in the laptop) and explain the data collected and used for analysis. If a reviewer guide is submitted together with datasets, explain the key part for datasets and variables.
- Pull out data listings according to requests from inspectors. Clinical and/or statistician will need to interpret and review the results.
- Check the data and compare with site source in HIS system or EDC. For example for certain subjects -
 - What is the discontinue date and reason?
 - How many visits?
 - Pull out certain lab tests.
 - Check if any medical history or concomitant medication recorded.
- Assist to answer questions or findings related to statistical analysis or study design
 - How allocation assignment is prepared?
 - How to impute missing value?
 - How is FAS population defined?

Central Lab

The main purpose of central lab inspection is to check the traceability to the source. The programmers need to assist the inspector to:

- Cross check the original records in lab database and lab data (LB or ADLB) used for CSR reporting, by random selecting a number of subjects and lab tests to check the consistence.
- Export lab data to excel spreadsheets for better filtering and displaying to inspector or other operation teams. For some lab tests (e.g. red blood cell or white blood cell), there will be multiple units and there is a need to explain the unit conversion if applicable.
- Cross check the lab records received by Lab for analysis and loaded in the database.

Bioequivalence (BE)/Pharmacokinetic (PK)

Two points outlined in the guidance by CFDI key points of site inspection for PK:

- Inspect the manual integration which impacted the AUC and Cmax.
- Analysis and calculation data and records of plasma concentration/pharmacokinetic/bioequivalence shall be reproducible on the corresponding software, and consistent with the summary report.
- The PK parameter calculation should be repeated on site and be the same as on CSR.

The PK parameters needed to be repeated using software (e.g. WinNonlin) and the descriptive analysis of PK concentration and PK parameter should match with results included in CSR. As the PK data is included in the submission package, we need to explain and explore the data to inspector if necessary. Further, for the data or subjects excluded from PK analysis, an explanation would be needed.

POST ACTION AFTER ON-SITE INSPECTION

Right after the on-site inspection, the sponsor will prepare the response according to the findings and communicate with CDE reviewer after the CFDI conclusion is announced.

Below are two main areas needed to produce updated analysis:

- Need to evaluate the impact of not valid data points
 - Exclude the related data points or the whole subjects in population and rerun the key analysis
- Need to evaluate the missing data (e.g. prohibited medication, missing AE, central lab issues) collected or entered in the data base.
 - Include the missing data and rerun and analysis (e.g. AE summary)

OTHER TIPS AND EXPERIENCE

- Provide the answers and inspection needs as fast as we can and make sure the accuracy and rationality. Perform fully validation before sending out the response or delivery.
- Do not provide extra additional data or information if not needed.
- Have good attitude to the inspectors (who has never seen your data before) and be calm and patient for any challenge or questions.
- Understand the different expertise from other teams (e.g. clinical, CRA) and learn from each other.
- Be prepared and collaborative to help the team.

CONCLUSION

The CFDI inspection requires sufficient preparation from understanding the detail data points to the final analysis result. The preparation process is straight forward and not complicate actually compared the regular statistical analysis during the study. But the preparation, supporting, and finding during the inspection will help us to think about what areas we can do better to improve the study operation and analysis in future.

CONTACT INFORMATION

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