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Key Statistical Programming Considerations in External Collaborative Clinical Trials

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ABSTRACT

Collaboration between pharmaceutical industry (sponsor) and external partners is increasingly popular in drug development as it can be mutually beneficial. While study activities from start-up to Interim Analysis are often performed by the external partner, who conducts the study, the collected study data is transferred to the sponsor to support a regulatory submission which requires CDISC compliant SDTM and ADaM datasets. This division of responsibility has created many challenges due to inconsistent data collection among partners, the quality or format of data used for Analysis and Reporting, and the timing to access the data by the sponsor for evaluation and transformation according to the regulatory requirements. This paper discusses some key statistical programming considerations, when working with an external partner, to improve the efficiency in data issue resolution, data transformation from raw datasets to SDTM and to ADaM, data compliance, blinding/unblinding processes, statistical report generation and submission package preparation.

INTRODUCTION

To expedite the innovative oncology drug development, collaboration between sponsor and external partners, such as external pharma/biotech companies, research institutes, academia, contract research organization, etc., is rising in popularity. It is common practice that the external partner conducts the initial study activities until the interim analysis (IA) or final analysis (FA) meets the study endpoint(s), and then transfer the collected data to the sponsor who completes the regulatory submission activities with required CDISC compliant SDTM and ADaM data packages.

In this collaboration, statistical programmers are faced with more complex operational challenges, including 1) high variability in data collection by partners; 2) high variability in applying industry standards by partners; 3) limited or no access to data during trial conduct resulting in considerable time and resource investment to get data in an acceptable format desired for A&R through multiple, necessary iterations of data transfers; 4) need for significant customization of sponsor's existing standard Analysis and Reporting (A&R) programs due to the lack of required variables or certain variable values; and 5) a significant amount of time needed for Trial Data Migration (TDM) and Data Analysis and Reporting activities, typically 12 to 18 months, because of working with data generated outside of Clinical Data Interchange Standards Consortium(CDISC) Standards (e.g CDASH, SDTM) and sponsor's standards and operating norm.

In such a competitive environment, SP team must collaborate with cross-functional stakeholders to proactively plan and adjust A&R practice to mitigate challenges so that studies with positive outcomes are not delayed in submission. This paper discusses some key considerations, when working with an external partner, to improve the efficiency in data issue resolution, data transformation from raw datasets to SDTM and to ADaM, data compliance, blinding/unblinding processes, statistical analysis, Tables, Listing and Figures (TLFs) generation and submission package preparation.

KEY STATISTICAL PROGRAMMING CONSIDERATIONS

In most of the external collaborative trials, the expectation for Statistical Programming (SP) deliverables is to meet the regulatory submission timelines and requirements after the full data is received. Therefore, statistical programmers' involvement with many front-loading activities through proactive planning is essential, e.g., data transfer and quality, timelines, A&R and regulatory deliverables. Details are discussed in the following sections.

DATA TRANSFER AND QUALITY

Collaborating with cross-functional stakeholders, SP team plays a critical role in the data transfer and quality (Figure 1) that has a direct impact on the success of partner trials. Depending on the type of the partnership, SP team may contribute to 1) protocol design and risk assessment on using the partner trial generated data for a regulatory agency submission; 2) evaluation of the data planned to be brought to the sponsor against industry standards, planned analysis and regulatory agency requirements; 3) data transfer requirements in terms of amount and frequency in the contract; 4) Case Report Form (CRF) design; 5) Data Transfer Specification (DTS); 6) TDM plan; 7) statistical analysis plan transfer, 8) program code transfer, etc.

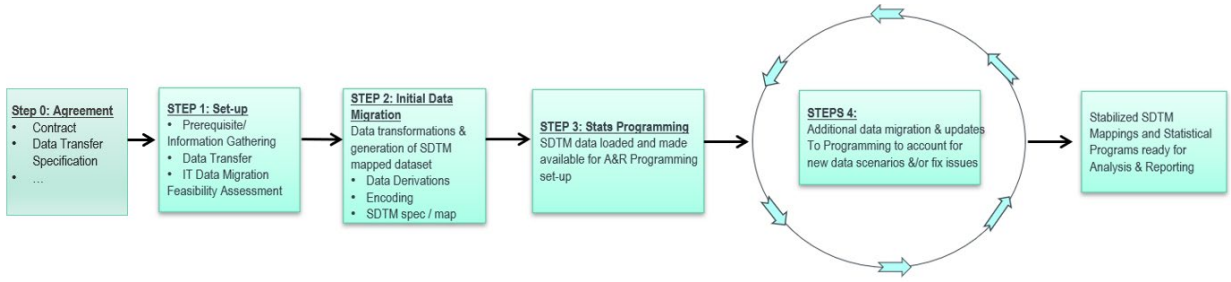

Figure 1 Data Migration and Statistical Programming Process

Many important topics need to be discussed during these activities. For example, timing of sharing patient-level study data after the study is closed to accrual, data transfer during accrual for preparation for possible regulatory submission, etc. It is ideal to have at least three data transfers from the partner to the sponsor before the Data Safety Monitoring Committee (DSMC) meeting, with

- first transfer of 10 - 20% subjects upon data available for the purpose of ADaM spec development,
- second transfer of 50% subjects with some tumor imaging data for table, listing and figures (TLF) development, and
- third transfer of 80 - 90% subjects include imaging data to prepare for clinical summary report (CSR) deliverable.

In reality, practice or agreement vary among partners in data quality, transfer frequency and amount. The required study data may not always be collected, such as adverse event (AE) verbatim terms, normal ranges for some lab tests that could post significant challenges to derive the lab toxicity grade and generate lab safety tables. The partner usually agrees to send the sponsor patient-level study data for five percent (5%) maximum or 15 to 30 study participants, whichever is lower, and start the transfer when all the study participants in the transfer have had certain follow-up period after randomization during data accrual. The timing for full data transfer could range from 30 to 60 days after the DSMC decision is made in favor of filing. Hence, the sponsor's SP team must evaluate the impact on the quality and timeline of A&R and submission packages and may need to develop a custom plan with unique timelines for each deliverable.

Regardless of the type of the partnership, SP team should always be proactive in the timely and ongoing communication with the internal study team and partner on raising questions and issues identified in the data received. This helps improve the efficiency of data issue resolution, safeguard data compliance, understanding, proper mapping and analysis. One of the key strategies is to transfer more comprehensive data from the partner earlier to help stabilize SDTM mapping and A&R programs prior to the decision for regulatory submission, to align quality with industry standards, ensuring that the submission is CDISC complaint and meets regulatory agency's requirements.

BLINDING/UNBLINDING PROCESSES

During the study process, the sponsor receives blinded/masked data to maintain study integrity. This is documented in the DTS, and it is partner's responsibility to ensure the blinded/masked data are transferred to the sponsor. However, blinding the data could be the responsibility of the sponsor, depending on how the contract is written. For open-label studies, partners often send unblinded data to sponsor to process.

Upon DSMC recommendation for regulatory submission, unblinded/unmasked data transfer activities are occurred according to the contract. SP team usually involves in the unblinding verification planning and perform the verification when partner's data are received. The unblinding verification may need to be done twice. Once it uses the raw SAS data transferred from the partner because the early result memo is produced with the partner's raw data, and then it is done on the SDTM data when the data mapping is completed. Specific programs may need to be developed due to different format of the raw data and non-standard allocation schedule file.

TIMELINE PLANNING FOR A&R AND REGULATORY SUBMISSION

Time needed for A&R and submission is usually significantly longer in an external collaboration trial comparing to an in-house study due to the tremendous effort required to communicate and map the raw data into industry complaint format, to customize the A&R programs, and to address the regulatory agency prerequisites. For the initial A&R specification setup, program development and validation based on the limited data for 15 to 30 study participants, it normally takes double or more amount of the time needed for an in-house study with more data. After receiving the full data with all data scenarios, it may still take the same amount of time as the initial setup to finalize the A&R programs.

SP team should build in all these additional activities into the timelines provided to the study team and make the team aware of the need for potential adjustment after evaluating the data received in each transfer .

A&R DELIVERABLES

For an external collaboration trial, standard ADaM data specification template, A&R macros/template programs, and TLF mockups always need to be customized owning to the data collection approach. To effectively define and derive the ADaM datasets and variables, SP team needs to consider the following:

Include analysis data point: Review the SDTM mapping specification to ensure data points needed for derivations and analyses are all included.

Understand partner's data: Read the related sections of the protocol and SAP and review CRF/aCRF to understand the data received.

Communicate effectively: Document the data questions, issues, and suggestions in the team tracker on an ongoing basis and meet with study team regularly for resolution. It is important to have the communication as early as possible as it may take longer time to get data issues resolved. For example, to update the WHO Drug Dictionary for concomitant medication variables.

Implement workaround: Utilize sponsor's A&R standards as much as possible, and meanwhile create specific variables required by TLFs but not available due to the data collection approach. For example, ADAE dataset cannot be used directly to generate exposure adjusted AE tables as AE records were collected differently. As a workaround, a special variable, AEPISODE, was created for calculating the number of unique AE episodes through collapsing AE records based on special rules. When TLFs required variables cannot be derived, request needs to be made for TLFs mockup update or a customized mockup.

Request analysis information: If the partner is responsible for submitting study results to DSMC, obtain program code or any related program documentation from the external partner, such as SAP, data set specifications.. Having well-documented program for reference can be helpful for the sponsor when performing any subsequent analyses. Analyses conducted on the migrated data must be consistent with the data in the primary publication produced by the partner.

REGULATORY SUBMISSION DELIVERABLES

Once the go-to-file decision is made, study team's expectation is to complete the regulatory submission activities as early as possible. Thus, various accelerated strategies may be proposed, such as Real-time Oncology Review (RTOR), rolling submission, and even non-CDISC compliant data packages. SP team needs to share the expertise and be actively involved in the discussion/decision to complete the submission with quality and compliance.

The submission components are often similar between the in-house and external collaborative trials. Since the sponsor does not own all the study data/documents, study team should discuss all the

deliverables expected to be in the submission package upfront. For example, site information is needed when BIMO package is included in the submission, patient CRF files might be provided to the sponsor by the partner for submission purpose, etc.

In addition, for source data issues identified by Pinnacle 21 but could not be resolved and any SDTM/ADaM variables deviated from the CDISC standards, they must be clearly documented in the reviewer's guides.

CONCLUSION

Conducting a collaborative clinical trial with external partner can be challenging yet rewarding. When it comes to statistical programming, it is essential to plan and manage all related activities strategically. Having the minimum required data in a desired format as early as possible, and meeting compliance requirements are the key to achieving the quality deliverables for a regulatory submission.

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