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Don't Sweat It! Consider Taking the Risk Out of Your Outsourced Deliverables

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ABSTRACT

In today's world, Pharmaceutical companies are consistently partnering with Clinical Research Organizations (CRO) for the creation of Statistical and Programming deliverables. Per ICH GCP 5.2.1[1]: A sponsor may transfer any or all of the sponsor's trial-related duties and functions to a CRO, but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor.[1] To successfully meet the ICH requirements, defining and documenting oversight are essential. When conducting oversight of CRO deliverables a risk-based approach is recommended. A risk-based approach involves a series of basic steps to perform a risk assessment for each study.

This paper covers a risk based approach for the following deliverables: Statistical Analysis Plan, Analysis Datasets, and Displays. These risks focus on complexity of analysis, experience with sponsor standards, novel endpoints/analysis and deviations. This paper will be helpful to all levels of programmers in the pharmaceutical industry, including lead programmers and managers.

INTRODUCTION

This paper presents key points to consider for Clinical Statisticians and Programmers (S&P) when conducting oversight of statistics and programming outsourced deliverables from Third Party Suppliers. We provide an overview of defining oversight and steps to provide a risk based approach to combine and leverage Quality Assurance and Quality Control practices to ensure that CRO deliverables meet sponsor expectations. For clarity, Quality Assurance is defined as a check on the process and Quality Control is a check on the specific results. Risks based questions for consideration are presented below in two parts, first are considerations at a study level which will impact the study in its entirety, next are deliverables based risk considerations which directed at specific risks for the given deliverable.

GENERAL CONSIDERATIONS

This section provides considerations Sponsors may take to demonstrate their oversight of outsourced deliverables.

- Consider contracting with a few "preferred providers". When establishing preferred providers, the sponsor should review key process and procedures to ensure alignment with Sponsors process and procedures. One of the key benefits of establishing preferred providers is their ability to consistently implement Sponsor's processes and procedures across the portfolio of work.
- To achieve proper levels of oversight Sponsor's should have a detailed plan on required documentation to demonstrate their oversight. This oversight plan should reflect the steps taken by statistics and programming to provide oversight to Third Party Supplier S&P teams. This plan should reflect the specific oversight activities for each study engagement and be documented for every study outsourced to the Third Party Supplier. The Sponsor is ultimately accountable for the deliverables, even when the statistical and programming tasks are outsourced to a Third Party Supplier. Therefore, the Sponsor must provide appropriate oversight of the Third Party Supplier to ensure that the results are accurate and all deliverables are of high-quality.
- To ensure proper alignment and escalation a formal governance structure between the Sponsor and Third Party Supplier should be established for risk mitigation and strategic objective considerations.
- To minimize potential risks all S&P Sponsor staff should be trained on the purpose of oversight principles. In addition, as part of general governance there should be a shared understanding with the Third Party Supplier on oversight principles and how they may impact the Third Party Supplier.

RISK BASED APPROACH AND STUDY CONSIDERATION

When conducting oversight of Third Party Supplier deliverables a risk-based approach is recommended.
A risk-based approach involves a series of basic steps to perform a risk assessment for each study.

Below are some study-level suggested risk-related questions for consideration in developing an oversight plan. The oversight plan will reflect the level of risk of each deliverable.

These risk factors would determine how much or what level of oversight would be required by the Sponsor overseer(s).

- Is the study a key or pivotal study within the asset (e.g. for Committing to Medicine Development, used for labeling purposes)?
- Is the study planned to be or likely to be included in a submission? Consider timing of the submission. Is it planned or imminent?
- Overall how experienced is the Third Party Supplier team with Sponsor studies (e.g. the clinical development phase, Therapy Area specific requirements, indication and/or with the asset or class of compound)?
- How global are the Third Party Supplier team?
- How complex is the protocol (i.e. fusion, complex primary/secondary analysis, exploratory)?
- How complex are the endpoints?
- How many vendors are providing data for the study?
- Are interim analyses planned? Will an IDMC/ARO be used?
- What could compromise compliance or data integrity and hence result in a major or critical audit finding?
- Have quality culture QC expectations been set?
- Will the Third Party Supplier provide a dry run of all analysis datasets, displays and CRT packages?

If any issues, errors or additional risks are identified whilst overseeing a study then the Third Party Supplier is responsible for putting a plan in place to fix the issues, errors and/or to mitigate the risks. Some example points to ask or consider are:

- Has the Third Party Supplier guaranteed fixing of issues for the next deliverable?
- Has the issue/error/ risk been escalated to functional governance committee?
- Has Third Party Supplier raised a Corrective and Preventative Action (CAPA)?

STATISTICAL ANALYSIS PLAN

The Statistical Analysis Plan (SAP) has various possibilities for outsourcing: SAP developed by the Third Party Statistician using the Sponsor's/Third Party SAP template and following Sponsor/Third Party Written Standards. Regardless of these options for outsourcing the SAP the Sponsor statistician should always act as a consultant to third party statistician during SAP development. In addition to consultation the current Analysis SOP/GUI/master templates and other relevant reference documents (e.g. Protocol, SRM, CRF) should be made available to the Third Party Statistician prior to the start of SAP development. The draft SAP should be reviewed by all appropriate Sponsor line functions including Sponsor statistician and Sponsor programmer. The Sponsor S&P and Third Party Supplier S&P teams should always participate in a SAP review meeting, to resolve any outstanding issues.
To document that the Sponsor has thoroughly reviewed and approved the SAP the Sponsor S&P leads should sign off on the final SAP. The below questions will help to determine how much risk there is to receiving a quality SAP, the more risk associated with the SAP development to more interactions between the Sponsor and Third Party Supplier will be required.

Examples of risk-based considerations:

- How complex is the analysis?
- Is the statistician familiar with the planned statistical methods of analysis?
- Has the programming team at the Third Party Supplier reviewed the RAP and provided sufficient questions?
- Is there a planned interim analysis? If yes, is a separate RAP for the interim analysis needed?
- Will there be IDMC review? Is there IDMC Charter?
- Are all the appropriate Sponsor and Third Party functions reviewing the RAP, not only S&P?
- Are all parties reviewing the RAP in a timely fashion?
- What are the milestones for finalizing and approving the RAP?
- If Sponsor written standards are being followed, is Third Party Supplier statistician aware of the critical components?

ANALYSIS DATASETS

The analysis datasets have several areas where risk can be introduced, first is surrounding the ADaM dataset specification and the second would be the ADaM dataset generation. An upfront consideration is whether the Sponsor will use the latest CDISC ADaM Implementation Guide or the Sponsor's version of ADaM specifications. A key point of communication between the Sponsor and Third Party Supplier are when deviations from either CDISC or Sponsor's ADaM specifications are necessary.

In addition, the Sponsor programmer/statistician should determine key algorithms/derivations, taking into account the importance and complexity of the study, the level of risk to Sponsor, and their confidence with the Third Party Supplier team.

Some ADaM dataset specification considerations for defining what is risk-based are given below:

Examples of risk-based considerations:

- Are the ADaM naming conventions being applied correctly?
- Are the Third Party Suppliers using the IG and/or Sponsor specs as required?
- Are the algorithms correct for defined variables?
- Are there any deviations from the standard ADaM format?
- Are there any TA/study specific domains?
- How frequently is the Third Party Supplier running PINNACLE 21 checks?
- Is the same version of ADaM being used as Sponsor's?
- Did any data collected impact any of the pre-defined algorithms?
- Could the data structure format comprise submission approval?

Some ADaM dataset considerations for defining what is risk-based are given below:

Examples of risk-based considerations:

- Are standard ADaM formats being used (ADSL, BDS, etc)?
- Are there new TA/study specific domains? (i.e. other complex and not previously programmed response criteria)
- How frequently is the Third Party Supplier running PINNACLE 21 checks?
- How are the Third Party Suppliers dealing with the errors and warnings in the Pinnacle 21 checks?
- Is Third Party Supplier following ADaM IG rules and guidelines?
- Is the same version of ADaM being used as Sponsor?
- Did any data collected impact any of the pre-defined algorithms?
- Are there Quality Control plans including study-specific checks?
- Is there complex statistical analysis that will require an ADaM dataset?
- Are there complex statistical algorithms?
- Is any data not planned to be databased?
- Have key values been checked for categorised derived values that may be subject to SAS floating point errors?

DISPLAYS

The displays (i.e. analysis tables/listings/figures) have several areas where risk can be introduced. A point of consideration is if annotated mock shells are value added, typically a Sponsor review of Annotated Mock Displays are most useful when programming is done on Third Party Provider systems. A key decision that needs to be identified is if Sponsor display templates will be utilized for the creation of analysis displays or if the Third Party Supplier's templates will be used.

Some display considerations for defining what is risk-based are given below:

Examples of risk-based considerations for annotated mock shells:

- Are the annotated mock shells reflecting the RAP or specifications?
- Are annotated variables referenced in dataset specifications?

Examples of risk-based considerations for displays:

- Have the displays been produced by Sponsor previously? i.e. is the Third Party Supplier trying to duplicate previously created displays?
- How complex is the primary/secondary analysis?

- If an error was found how likely is to impact the results of the study?
- Have significant errors been found previously?
- Were there any data outliers or protocol deviations to be excluded from analyses?
- Were there any deviations to the planned analyses?
- Was the study randomized? Are the treatment effects in the expected direction?
- Do the results make sense i.e. figures consistent with tables, number of subjects as expected, consistent use of symbols and colors in figures, overall consistency across the package.
- Are the Third Party Supplier aware of the process to follow if an unexpected safety issue is identified during reporting (i.e. escalate to Sponsor statistician)?

CONCLUSION

Overall, oversight and risk based points to consider are key to ensuring that both the Sponsor and Third Party Supplier are aligned with expectations and delivering quality outputs. As ICH requires, the Sponsor is accountable for ensuring the quality and the integrity of the data and subsequent analysis. To facilitate this accountability the recommendation is to determine the key risks associated with the study and deliverables to maximize oversight tasks. When conducting the risk based assessment, documentation is key to demonstrate compliance with ICH.

REFERENCES

[1] International Council for Harmonisation Efficacy Guidelines (ICH). Accessed November, 2016. http://www.ich.org/products/guidelines/efficacy/article/efficacy--guidelines.html

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