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Identifying Sponsor Checks of Outsourced Deliverables

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ABSTRACT

As the Sponsor, when receiving outsourced ADaM datasets and analysis displays for review, is a full double programming the best method to guarantee the integrity of those deliverables? With timelines set and deadlines approaching, it is a best practice to decide prior to review what programmatic checks will yield the greatest insight into the quality of the deliverables received from the contracted Third Party Supplier. In accordance with ICH GCP Section 5.2.1 "...the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor." In this paper, we will outline a method to define those programmatic checks. The purpose is to provide insight for effective review of outsourced deliverables. We will combine quality assurance and quality control to meet the needs of Sponsor oversight and adherence to ICH GCP.

INTRODUCTION

The following content includes two major sections with regards to analysis oversight of a Third Party Supplier. First, we describe our method to strategize your oversight activities. We will introduce a categorical approach to dividing your review of analysis datasets and TFLs. This approach will aid you in time management of yourself as a clinical programmer or your clinical programming team, as well as, a programmer's skill level to consider for each review category. Next, we outline an oversight planning method that includes an array of topics for successful management of oversight activities. When these topics are combined, they produce a complete picture of oversight interaction with your Third Party Supplier.

As stated in the above abstract, the "purpose is to provide insight for effective review". By breaking down what an "effective review" means into the Strategy scope and the Planning scope components, we are providing you detailed information on how to effectively manage your oversight and conduct your oversight. Details at each level give you applicable information to apply now. We include a short take-away Checklist in **Appendix 1** that you can print. It lists the major points to oversight planning and can be used to launch your oversight planning activities.

ANALYSIS OVERSIGHT STRATEGY

To determine what oversight should be applied to the outsourced ADaM Datasets, the analysis programmer should review the Statistical Analysis Plan (SAP) along with the dataset specifications. All variables needed to produce the TFL outputs should be present at the ADaM dataset level. Take note of variables that will be used to create the headline (or top-line) outputs. These variables are closely tied to measuring the primary and secondary objectives, and they will best be reviewed through independent programming by the sponsor. This allows both the Sponsor and Third Party Supplier the opportunity to cross-check the variable's algorithm as interpreted from the SAP. Use the variables described in this paragraph to identify the high priority datasets. Then, a strategy should be discussed on how to approach the remaining datasets and TFLs in the analysis package.

For this strategy, we have divided them into 3 risk categories and each category represents an approach to checking the quality of those deliverables. The three categories are: standard ADaM deliverables (*Standard*), typical ADaM deliverables to the therapeutic area (*Typical*), and atypical ADaM deliverables to the therapeutic area (*Atypical*). These categories represent *Standard* (low), *Typical* (medium), or *Atypical* (high) programmatic attention for coding study specific variations.

REVIEW OF STANDARD DATASETS AND TFLS

Standard datasets have the least amount of specification structure variation across studies and the corresponding TFLs would be considered standard, as well. Examples are ADCM, ADDS, ADDV. For this category, checks can be automated using macros. If the dataset specification file can be read in as a dataset, use this dataset to compare against the received deliverable as a front-line check. Confirm all variables are accounted for and store the length



and label values into macro variables. The macro variables can then be compared to a `proc contents` of the deliverable dataset from the Third Party Supplier.

Date Imputation Flags can be confirmed within a macro check by comparing the analysis dates to the SDTM dates with the existence of the imputation flag = Y. Study specific post-processing that may need to be added includes derivation for Phase/Period assignment, unique flags, or analysis timing reference variables. If the dataset is given thorough review there should be minimal time requirements for quality review of the corresponding TFLs. `Proc Freq` tables should allow you to identify the counts for specific population subsets.

REVIEW OF TYPICAL DATASETS AND TFLS

Typical datasets are always or often present within individual therapy areas (TA). Virology datasets are an example of a typical dataset to the Infectious Disease TA. We place ADSL in the *typical* category too. Often, the added variables to ADSL outnumber the common (or core) ADSL variables. These custom ADSL variables trend within a therapy area (or even more at the compound level) and very few variables fall into the grouping of strictly study specific. Often, referencing past studies within a therapy area can set a strong foundation of ADSL grouping, count, or flag variables. Like *Standard*, *Typical* datasets can utilize a macro for commonalities among study design within a therapy area or within a specific compound.

Automating frees up time and energy for the sponsor's clinical programming team to hone-in their review to the variables at the core of measuring primary endpoints, safety, and efficacy components of the trial. For all automated checks, a complete review by the sponsor's clinical programming team is required to maintain the associated risk with each deliverable category. Just because an activity is automated using macros, does not eliminate the importance for checking log files and looking at the entire report generated. Failure to thoroughly review automated checks leaves the door open for the potential to miss errors in programming or data anomalies by the sponsor.

For the review of *typical* TFLs, again with a strong dataset review strategy there should be minimal time requirements for quality review of the corresponding TFLs. Their mock shell is also common within the therapy area and the needed ADaM variables show consistency across input analysis datasets. Here you may find `proc freq` and `proc means` should allow you to produce and compare the values to the TFLs produced by the Third Party Supplier.

REVIEW OF ATYPICAL DATASETS AND TFLS

So now we come to the category of atypical deliverables. These datasets and outputs can be compound specific and/or single study specific. Their review should receive a high priority status which we interpret as: includes critical components for correctness and accuracy of the trial headline (or top-line) reporting when trial analysis is deemed complete. To truly ensure atypical deliverables are correct, we recommend they receive the most time allotted for complete independent programming by the sponsor. In this category, many of the TFL outputs capture primary and secondary endpoints, along with dosing compliance data. Full double programming done by the sponsor for this category opens the way for any questions or debate of design, interpretation from the SAP, algorithm design inquiries to arise between sponsor and contracted party. Allowing time for debate among sponsor and contracted teams can be helpful to highlight issues or work out design details possibly overlooked or only recently applicable as new data cuts are added.

STRATEGY CONCLUSION

A strong reason for a sponsor's clinical programming team to strategize their oversight of a Third Party Supplier in the manner we have described above is: to reserve yours (or your team's) time, energy, effort, and thought to the review of the atypical deliverables with the importance of debate and questions. It is the inclusion of multiple perspectives that develops and delivers a robust analysis package. Thinking all the way through the process and discussing with colleagues lowers the risk of missed errors.

ANALYSIS OVERSIGHT PLANNING

HOW TO SETUP FOR SUCCESS

- Set correct (or to your best knowledge) expectations
 - Let your Third Party Supplier know the correct scope of work and timelines. Granted things change in real-time but share all available information on time.
- Have necessary documentation ready that the Third Party Supplier needs to start and progress work.
 - Examples include: SAP, protocol, any other guidance material, etc.
- Set realistic timelines after conversation with the contracted party.
- Deduce the programming support needed on both sides (Sponsor and Third Party Supplier) ahead of time.



- Setup intermittent timelines for small packages of delivery
 - Examples include: Safety, Efficacy, PK, Datasets, TFLs, etc.
 - Treat the intermediate timelines as seriously as the final timeline.
- Have repercussions spelled out in the contract for poor quality and/or missed timelines.
 - The intent should not be to use it but having it in the contract keeps the contracted party accountable for their work.

TRACKERS

- A QC plan is a document that has all the components of the study
 - Example shown in Figure 1
 - Could include: datasets, TFLs listed out with associated information such as, programmer names and dates work occurred
 - QC Plan should be updated on a regular basis and should be stored where both Sponsor and Third Party Supplier have access to it.
 - If possible have % complete calculated in the sheet to enable a quick status check.

Data Group	Display Section	Display Type	Display Number	Display Title	Target Date	Actual Date	Target Date Passed QC	Date Passed QC	Overall
ADSL	Study Population	Table	1.1.	Summary of Study Populations	22-Feb-18		#####		#####
ADSL	Study Population	Table	1.2.	Summary of Subjects by country and investigator	22-Feb-18		#####		#####

Figure 1: Figure of a QC Plan

ISSUE AND DECISION TRACKER

- The Issue and Decision tracker is a document that maintains the flow of communication between Sponsor and Third Party Supplier outside of regular scheduled meetings. See Figure 2.
- Both parties can put their questions and findings, or responses in the tracker.
- The tracker should be reviewed/answered on a regular basis and within a reasonable period to enable timely progress.

GSK Stats/Stats Programming FSP: Oversight Issue Tracker														
Status	Count													
Open	0	GSK Lead Statistician	xxxxx											
In Progress	0	GSK Lead Programmer	xxxxx											
On Hold	1	Other GSK Resources	xxxxx											
Escalated	0	Quanticate Lead Statistician	xxxxx											
Closed	112	Quanticate Lead Programmer	xxxxx											
		Quanticate Team	xxxxx											
Ref #	Impact	Type Issue / Action	Issue / Action / Risk Description	Further details	Status	Raised by	Raised Date	Assigned to	Due Date	Escalated to	Closed Date	Resolution Actions	Solution / Decision	Comments

Figure 2: Figure of the Issue and Decision Tracker

MEETINGS: COMMUNICATION IS KEY

Kick off Meeting:

- Set a kick off meeting ideally a couple of weeks before the start of programming.
- The idea is to introduce the study, timelines, contact person from other departments and expectations for the length of the study to the team.
- Take down meeting minutes and save it for future reference.

Status Update Meetings:

- Set up weekly or bi-weekly meetings to have dedicated time to discuss study related matter.
- Always have an agenda prepared and shared ahead of time.
- Keep time to discuss Status Updates and time for Third Party Supplier study related questions / confusions.
- Take down Meeting Minutes and ACTION Items
- Send meeting minutes in a timely fashion to allow time for review and work on action items.
- Hold parties accountable for their tasks and actions.
- During every meeting ask your contracted party for a status update, including % of work complete up to current time point and progress from the past week.
- Optionally, have a timekeeper and a rabbit hole monitor to keep the meeting on point and avoid digressing from the current topic.



PROGRAMMING TEAM

- Try and have the same set of personnel on the study from start to finish.
- Ensure that the personnel have the required training to do the job ahead of start of study.
- Have a mix of programmers. Ensure a staggered experience level of programmers, including junior to senior levels.
- Having one or two programmers who have worked on a similar study before helps.

TIME OFF

- Time off is important and should be supported.
- Maintain a sheet that records personnel time off.
- Have a backup ready for the Sponsor and the Third Party Supplier personnel.
- Also, proper communication/reminders should roll out when someone plans to go on vacation.

CONCLUSION

We have detailed the two primary components to successful oversight of your Third Party Supplier: oversight strategy of activities and oversight management planning. Combined, they deliver a robust program for assuring the quality of ADaM datasets and analysis TFLs delivered to you for sponsor review. For the strategy component, a practical assessment of the datasets and TFL priority levels and then categorizing them according to their proximity to measuring the protocol endpoints, inclusive of safety, efficacy, and monitoring dosing compliance. In the planning portion, your prep is key to setting a strong course of action for completing your reviews effectively and within timelines. We provide multiple sources for what to have and way to use tools, along with a quick checklist in **Appendix 1**. Thank you for taking the time to read our content and you are welcome to contact us with any question using the below contact details.

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the authors at:

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APPENDIX1

Quick Comprehensive Checklist

- ☐ Have study folder setup
- ☐ Copy in all necessary standard macros
- ☐ Save study related material in the study folder. Eg: SAP, Protocol, etc.
- ☐ Save any / all required company specific templates in the study folder. Eg:
Template for Meeting Minutes, etc.
- ☐ Create a Timelines sheet.
- ☐ Create Study Specific QC Plan with current study information.
- ☐ Create Issue and Decision Tracker with current study information.
- ☐ Team Personnel Contact List
- ☐ Create Time-off Calendar
- ☐ Send out Regular Meeting Invites with the Internal team, as well as, Third Party
Supplier team