

Don't Sweat it!

Consider Taking the Risk Out of Your Outsourced Deliverables

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SP11

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- Why is Oversight Important?
- Relationship building Considerations
- Examples/Oversight Risk Based Considerations
 - Overall Study
 - SAP
 - Analysis Datasets
 - Displays
- Risk Based Documentation

Q and A

Why is Oversight Important?



- **ICH GCP 5.2.1:** 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.
- **Adherence to Sponsor SOP's.**
- Lack of **documented evidence** of Oversight poses a risk of a **regulatory finding**.

- For S&P we define QA/QC as the following:
 - Quality Assurance (QA) – is a check on process
 - Quality Control (QC) – is a check of specific results
- Oversight is providing a risk based approach to combine and leverage QA and QC practices in order to ensure that the third party has delivered to Sponsor expectations.
 - **A Risk Based Points to Consider** will assist in leveraging these two concepts.
- Since ultimate accountability resides with the Sponsor they must have effective oversight of the third party vendor and demonstrate evidence to support such oversight.
 - **An Oversight Plan template** could help demonstrate your oversight evidence.

Relationship Building Considerations

Relationship Considerations

Qualifying Third Parties



- Consider contracting with a few “preferred providers”
- Evaluation of whether the Third Party is able to meet the **technical** requirements of the work being outsourced to the quality and timeliness as **defined by the Sponsor**.
 - Reporting System; Sponsor vs Third Party
 - SOP's: Sponsor vs Third Party
 - Analysis Specifications(data sets and displays):Sponsor vs Third Party
- 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.

Examples of Real Life Oversight

Example of a FTiH study



A randomised, double blind (sponsor unblinded), placebo controlled, parallel group, single ascending dose study to investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics of Sponsor dose in healthy volunteers (Phase I Study)

- CDISC study
 - SAP, datasets and displays have been outsourced to Third Party Provider
 - Third Party Lead Programmer and statistician are experienced, and have expertise in early phase studies and Sponsor studies
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Study Level - risk-based considerations



- 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 QC expectations been set?

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- 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 SAP and provided sufficient questions?
 - Is there a planned interim analysis? If yes, is a separate SAP for the interim analysis needed?
 - Are all the appropriate Sponsor and Third Party functions reviewing the SAP, not only S&P?
 - What are the milestones for finalizing and approving the SAP?
 - If Sponsor written standards are being followed, is Third Party Supplier statistician aware of the critical components?

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- Do you have confirmation from the conversion lead or data manager that the Sponsor standard algorithms were used?
 - 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 QC 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?

Example of a FTiH study



A randomised, double blind (sponsor unblinded), placebo controlled, **parallel group**, single ascending dose study to investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics of Sponsor dose in **healthy volunteers** (**Phase I** Study)

- CDISC study
- SAP, dataset and display deliverables outsourced to Third Party Provider
- Third Part Lead programmer and statistician, **experienced**, and expertise in early phase studies and Sponsor studies

Based on initial assessment no major risks were identified for this study.

Example of a FTiH study



Over time...

- First review of the S&P deliverables (at first dry run for interim) –
 - Quality concerns around Displays (incorrect population was used for a primary end point display)
- ⇒ Sponsor S&P believe that the risk level has increased based on risk-based points to consider

Protocol: ABC123456

Population: PK

Listing 2.1
Listing of All Adverse Events

Treatment Group: Placebo

Inv./ Subject ID	Age (y)/ Sex/ Race/ Weight (kg)	System Organ Class/ Preferred Term/ Verbatim Text	Onset Date/ Resolution Date/ Duration	Time Since 1st Dose/ Time Since Seric Last Dose	Inter Outcc
100780/ ABC123456.000013	15/ Female/ WHITE - WHITE/CAUCASIAN /EUROPEAN HERITAGE/ 65	Injury, poisoning and procedural complications/ Concussion/ HEADACHE SECONDARY TO CONCUSSION	2014-08-02/ 2014-08-11/ 10 d	26 d/ 9 d	MILD/ No/ RECOV SOLVE

- 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 randomised? 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 colours 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?

Example of a FTiH study

Over time...



- After the risk-based assessments these are the **potential outcomes**:
- First review of the S&P deliverables (at first dry run for interim) - Quality concerns around Displays (incorrect population was used)
 - Sponsor S&P believe that the risk level has increased based on risk-based points to consider
 - Regular joint S&P meetings
 - Increased the number of deliveries (an additional dry run was added)
 - Added additional independent QC of key primary endpoints

Risk Based Documentation

S&P Oversight Documentation

Oversight Plan, Kick off Meeting Minutes, Meeting minutes



- Oversight Plan
 - Provides a mechanism for documenting **how oversight was provided** and also for **tracking issues identified** during Sponsor's review of CRO deliverables (e.g. TLF datasets).
 - Separate tab (if in excel) accessible only to Sponsor staff which contains specific study level checks
- Kick Off Meeting Template (KOM)
 - Consists of suggested topics for consideration when meeting with the CRO prior to start of work. .
- Meeting Minutes Template
 - To document discussions, agreements etc. made by Sponsor/FSP/FSO during the course of a study/project (allows to demonstrate oversight)
 - Meeting minutes are required but part of the KOM should be who will take the meeting minutes, as it is completely acceptable for FSP/FSO to be accountable for taking meeting minutes.

A	B	C
	Deliverables	Comments
	(*Note: Standard text should remain in this column and any differences noted in the 'Comments' column)	
RAP	Reporting and Analysis Plan (including mock shells)	Not Applicable
RAP	Reporting and Analysis Plan will be developed by the FSP/FSO Statistician using the GSK/Third Party RAP template and following GSK/Third Party Written Standards.	
RAP	GSK Statistician will act as consultant to FSP/FSO statistician during RAP development.	
RAP	Current RAP SOP/GUI/master templates and other relevant reference documents (e.g. Protocol, SRM, CRF) will be made available to the FSP/FSO Statistician prior to the start of RAP development.	
RAP	The RAP must be developed using the current master RAP Template.	
RAP	Draft RAP will be reviewed by all appropriate GSK line functions including GSK statistician and GSK programmer	
RAP	A RAP review meeting will be held to resolve any outstanding issues if needed.	
RAP	The GSK Statistics & Programming TA Manager (or delegate) and all appropriate GSK line functions will technically approve the final version of the RAP.	
RAP	The above process will be applicable to the critical components and full RAP.	
◀ ▶ Title Page Deliverables Reporting Checks (GSK ONLY) Datasets Displays CRT Package Stage 2 QC Stage		

Reporting Checks tab



A	B	C
Study Specific Oversight Checks (<i>Suggested considerations</i>): Any findings from the GSK Stage 2 QC should be documented in the Datasets/Displays/CRT Package Tabs where appropriate.		
SDTM Datasets (<i>What variables are derived, what impact will it have on analysis, has dm confirmed if there are any deviations from global specs, etc?</i>)		
derived variable 1		
derived variable 2		
derived variable 3		
ADaM (or AR) Specifications (<i>Have there been any deviations from the GSK approved specifications, has there been a thorough review between RAR and specifications?</i>)		
ADSL, ADDS and ADAE - checked that standard macros were used		
	Title Page	Deliverables
	Reporting Checks (GSK ONLY)	Datasets Display
ready		

	A	B	C	D	E	F	G	H	
1						GSK Comments			
2	Table/Figure/Listing	Section	Number in RAP	Display number	Title	Comments	Reviewer	Review Date	Resc
3	Listing	Safety	2.1	2.1	Listing of All Adverse Events	PK population has been used instead of Safety	BB	01-Jan-17	

Navigation: Title Page | Deliverables | Reporting Checks (GSK ONLY) | Datasets | **Displays** | CRT ... (+) | ...

	A	B
	Study Specific Oversight Checks (<i>Suggested considerations</i>): Any findings from the GSK Stage 2 QC should be documented in the Datasets/Displays/CRT Package Tabs where appropriate.	
5	Displays (T/L/Fs)(<i>How big of an impact will TLF have on study results?</i>)	
5	Population of all the primary end point displays was checked	
7	Review displays for formatting issues, misspellings, obvious errors, and outlier values (such as negative durations)	
	Code Review - are standard macros being utilized where appropriate, is code well commented	

Navigation: Title Page | Deliverables | **Reporting Checks (GSK ONLY)** | Datasets | Di

Q&A