PharmaSUG 2019 - Paper SI-142

Sponsor Oversight – Proof is in the documents

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ABSTRACT

Increasing number of biotech and pharmaceutical companies are conducting clinical trials by either partially or completely outsourcing clinical trial activities to third party organizations (e.g. Contract Research Organizations (CROs) and Clinical Trial Units (CTUs)). There is a clear requirement according to ICH GCP (Good Clinical Practices) E6(R2) that the sponsor must have systems and procedures in place to ensure adequate sponsor oversight. Failure to comply in this area can result in critical findings in regulatory inspections and also prevent the organization from sponsoring any further trials until the issues are resolved. This paper will discuss in detail about the different documents that the biostatistics and statistical programming team at the sponsor can use as evidence to prove sponsor oversight. These documents will help the sponsor in conducting oversight as well as will improve the inspection readiness of the sponsor. This paper will also briefly discuss about good documentation practices for maintaining these documents and how they can improve the effectiveness of sponsor oversight and provide evidence to prove sponsor oversight.

INTRODUCTION

On 15 December 2016, the International Council for Harmonization (ICH) adopted the revised E6(R2) guideline, entitled “Integrated Addendum to ICH E6(R1): Good Clinical Practice E6(R2).” Now, regulatory implementation is carried out according to the same national/regional procedures that apply to other regulatory guidelines and requirements (ICH 2017).

The ICH E6(R2) addendum affects the full clinical trial cycle and research enterprise. The revisions to the guideline mainly affect sponsors, stipulating a more proactive approach to study design, as well as risk management and study monitoring.

One of the focus of the revision is specifying oversight responsibilities of sponsors. As stated in the previous guideline, the sponsor is still permitted to delegate trial-related responsibilities to others (for example, contractors and vendors), but the sponsor is ultimately responsible for the quality and integrity of the data and the analysis. The revised guideline adds, in section 5.2.2, that the sponsor should ensure oversight of trial-related duties and functions carried out on its behalf, even for those responsibilities subcontracted to another party by the sponsor’s contracted CRO (ICH 2016). The sponsor must plan and describe how this will be assessed. Sponsor should provide evidence for the oversight. The following sections will describe different documents that can be produced during the conduct of clinical trial by sponsor statistical programmer that can show sponsor oversight. These documents will also help the sponsor in ensuring proper oversight.

PARTNERSHIP MANUAL

There should be a document explaining the roles and responsibilities of each function for each activity in the partnership using responsibility assignment matrix (RACI charts) and swim lane diagrams/ flowcharts. This document should be a controlled document and all the functions should be trained on this document.

Table 1: RACI chart

Process	Sponsor Biostats and Programming	Vendor Biostats and Programming	Data Manager	Clinical/ safety teams
Annotating CRF	A	R	C/I	
SDTM datasets	A	R	C/I	
ADAM specs	A	R		C/I

R = Responsible A = Accountable C = Consulted I = Informed

So as seen in the above Table 1, Biostatistics and programming group is accountable for the final quality of all the analysis. The chart shows that the vendor is responsible for creating the outputs.

In the swim lane diagrams, the partnership manual can describe in detail about the process flow regarding who will initiate the process, and how it will move from the vendor to the sponsor for oversight and showing the feedback path for the vendor to make updates to the deliverable depending on sponsor comments.

OVERSIGHT DOCUMENTS

RISK ASSESSMENT OF STUDY

The study statistician and the statistical programmer will assess the complexity of the study and following a risk based approach determine which data points will determine the accuracy of the primary and secondary endpoints as well as the safety endpoints. The document will determine what level of sponsor oversight is needed for the study and which data points and analysis is of interest or at higher risk.

For example a Phase 3 Pivotal study might be high risk which will require much more sponsor oversight while a post marketing study might be considered a low risk oversight which will require a standard sponsor oversight. The study statistician will make judgement on the level of oversight is needed.

OVERSIGHT PLANNING DOCUMENTS

SDTM and ACRF Review Checklist (internal sponsor document)

A checklist with all the quality checks that can be performed to check the quality of the SDTMs can be created. These checks can be classified into checks required for study requiring extended oversight and checked required for study requiring standard oversight. Depending on the risk assessment the programmer will plan to implement these checks.

Different checks that can a part of this list can be:

Checking number of observations from raw datasets against observations in corresponding domains.

Checking if all the required variables are present in each domains.

Check the derived SDTM variables in each domain.

Checking the Pinnacle 21® report for errors and warnings.

Checking the “NOT SUBMITTED” fields on the annotated CRF.

Checking annotated CRF to ensure all the data points are mapped in the correct domain.

Checking lab conversions.

ADaM and TLF Validation Plan (Internal sponsor document)

A QC plan describing in detail which ADAM datasets/variables will be reviewed and what kind of QC checks will be performed can be prepared by consulting with study statistician. This plan will also contain a list of Tables and Figures that need to checked with double programming. This list generally contains top line results and can be longer or shorter depending on the risk assessment of the study.

ISSUE LOG (To be shared with vendor)

After the SDTMs are reviewed as per the QC Checklist and ADaMs and TLFs are reviewed as per the QC plan, the issues identified by the sponsor’s statistical programmer will be entered in this Issue Log. This Issue log will then be shared with the vendor. The vendor will then fix the identified issues or give an explanation regarding why a particular issue exists. At the end of the study all the issues should either be fixed or sufficiently explained.

Table 2: Issue Log

Issue ID	Date	Deliverable	Dataset / TLF	Issue Detail	CRO Programmer	Resolution
1.	02JAN2019	SDTM	DM	Please check RFSTDTC derivation	ABC	Fixed
2.	02JAN2019	Acrf	Page 4	Please map xxx field to XX Domain	ABC	Fixed
3.	02JAN2019	ADaM	ADSL	Please check FASFL derivation	ABC	Fixed
4.	02JAN2019	Tables	Table 14.2.3	Please check xxx values	ABC	This is due to reason XYZ, the decision was taken at the meeting on xxxx, the meeting minutes are saved in TMF.

This issue log can also be used as a reference while creating analysis dataset reviewer's guide (ADRG) and study data reviewer's guide (SDRG) to explain outliers and deviations from the statistical analysis plan (if it exists).

SIGNOFF SHEETS

After all the final deliverables are received by the sponsor a signoff sheet stating the details of the deliverable will be filled up and signed by sponsor and vendor biostatistics and programming team members.

DATA TRANSFER AGREEMENT / ACCEPTANCE FORMS

A data transfer agreement should be created to detail the mode of transfer, the content of the transfer. A data transfer acceptance form should be signed by the sponsor to confirm that the agreed upon deliverables are received. Such documents are useful to track the data transfers that occur between the sponsor and the partner. File checksum / file identifiers should be created that can be used to maintain traceability.

CONCLUSION

Documentary evidence needs to be created by the sponsor showing that enough oversight was performed on the activities performed by the CRO. Such documents will help in inspection readiness and can also help the sponsor for conducting effective oversight. All the above documents will be part of the trial master file at the end of the study.

REFERENCES

INTEGRATED ADDENDUM TO ICH E6(R1): GUIDELINE FOR GOOD CLINICAL PRACTICE E6(R2) https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4_2016_1109.pdf

ACKNOWLEDGMENTS

The author will like to thank Rui (Sammi) Tang from Servier Pharmaceuticals for their encouragement and support.

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