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Sponsor Oversight of CROs Data Management and Biostatistical Abilities

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ABSTRACT

Sponsors of phase I, II and III Clinical Trials who partner with full-service CROs for the management of a clinical trial are responsible for data quality and integrity; choosing a CRO is a critical decision on the way to FDA submission. In my experience, full service CROs tend to be chosen based on their competence in their clinical operations department that recruits study sites and cares for patients. The mission critical oversight and connection with the biostatistics and data management departments tends to be an afterthought, yet these teams provide the study documents and data submission package required for pharmaceutical compound submission to the FDA. This paper highlights key considerations for data management and biostatistical services from a full service CRO starting with the bid defense meeting through study conduct and final deliverables.

INTRODUCTION

See Table 1 for a list of abbreviations used throughout this paper. The first check of a CRO's competence is to evaluate their understanding of the rules of conduct for clinical studies. Internationally focused clinical research has written rules to follow: ICH-GCP, Declaration of Helsinki, GMP, GDP, Local Regulations and guidelines. The United States requires compliance with the following guidelines for an FDA submission: GCP, GLP, eCTD and ICH E9. Whether a sponsor needs a quick turnaround time that can be facilitated by round the clock work then maybe a CRO on the other side of the globe that speaks your language is a good fit. On the other hand if a sponsor wants to communicate with the CRO during regular office hours then keep that consideration in mind when choosing a CRO to work with.

Small biotechnology company sponsors of clinical trials may have none, or just one or two staff members familiar with these rules that serve as a biostatistician and data manager to review and oversee a CRO's abilities to deliver quality study planning documents and data sets for an FDA submission. With limited in-house sponsor resources, study sponsors need to be laser focused on the key elements that provide quality deliverables for a successful FDA submission. More importantly, when an FDA inspector comes to visit the sponsor, the sponsor needs to be able to say with confidence that the CROs did what the Sponsor asked them to do.

Sponsors can choose from a few thousand CROs with various levels of competence, expertise and technology use and gets many advantages from working with a full service CRO to complete a clinical trial. The CRO is an independent company that is conducting the study thus reducing the chance of sponsor bias. A sponsor's staff can be expanded or contracted by contracting with a CRO, as needed. Most importantly, the full service CRO will connect and coordinate communication across each of the key team members and departments listed in Table 2. Sponsors can begin by identifying three CROs with the needed clinical expertise; welcome each team to visit the sponsor to showcase their expertise. Then ask for three references from each CRO to get an idea of their work style. The key elements of a successful Sponsor-CRO partnership include CRO management competence, minimal third-party partnering and knowledge of CDISC standards.

LIST OF ABBREVIATIONS

Abbreviation	Explanation
ADaM	Analysis Data Model
ADRG	Analysis Data Reviewer's Guide
CDISC	Clinical Data Interchange Standards Consortium
ClinOps	Clinical Operations
CRF	Case Report Form
CRO	Clinical Research Organization
CSR	Clinical Study Report
DMP	Data Management Plan
DSC	FDA Data Standards Catalog

Abbreviation	Explanation
DTA	Data Transfer Agreement
eCRF	electronic Case Report Form
eCTD	electronic Common Technical Document
FDA	Food and Drug Administration
GDP	Good Distribution Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH E9	International Conference on Harmonization Statistical Principles for Clinical Trials
ICH-GCP E6	International Conference on Harmonization - Good Clinical Practice
IG	Implementation Guide
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
PK	Pharmacokinetics
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System
SDTM	Standard Data Tabulation Model
SDRG	Study Data Reviewer's Guide
SoA	Schedule of Assessments
TLF	Tables Listings and Figures
UAT	User Acceptance Test

Table 1. List of abbreviations used throughout this paper.

BID DEFENSE MEETING

The bid defense meeting is organized by the sponsor's ClinOps department for a mutually convenient time for the key senior CRO staff members to present, usually a slide presentation accompanied by discussions for clarification about their shop's expertise. As a sponsor we look for

- experience at all levels of management for your specific therapeutic area and the drug's indication
- the clarity with which the team leaders are able to explain their team's work
- their usual timelines for deliverables
- in-house hardware and software use and years of experience with both
- staff retention rate, cumulative or minimum years of experiences by staff, and well-seasoned staff with across discipline experience and/or understanding

Red flags of caution are

- use of paper CRFs, that lacks automation for real time reviews
- one business manager monopolizes the conversation to cover for other team members lack of experience
- the number of staff members relative to the yearly work load just doesn't seem possible
- a key leader is absent, for example, the statistician
- company buyouts that live off the reputation that precedes it

Signs of an effective and thoughtful team environment

- a presentation personalized to the Sponsor's protocol needs with insightful suggestions for improvement
- when team members talk with each other to share ideas in response to questions, it shows that the different departments are working well together

- software use with real time tracking and electronic alerts of study quality metrics to anticipate problems and resolve them quickly

The cost of a CRO's services weighs heavily for a startup biotech company and is less of an issue for a large company sponsor. When the sponsor can find a CRO that they work well with and can provide about two or three short term studies a year then that CRO may be able to provide a more reasonable price and be able to dedicate a team to your projects based on the volume of work. A good working relationship tends to work for as long as you have your "work well together 'A' team" in place. Staff turnover can change this in an instant. When this happen and a sponsor notices quality slipping, it is important for sponsors to know who to escalate this concern to in the CRO organization as soon as possible to not compromise the quality of your final deliverables. To this point, a sponsor with at least one experienced statistician and one experienced data manager in house to understand and oversee the work of a CRO is mission critical.

STUDY TEAM MEMBERS

Table 2 lists the key CRO team members for a successful clinical trial needs to be qualified by training and experience to fulfill the responsibilities of project manager, medical monitor, clinical monitors, data managers, biostatistician, statistical programming and medical writer. Subcontract vendors are sometimes needed for example for the IVRS / IWRS system, clinical laboratory data, PK laboratory data and drug importation. Characteristics of interest are sometimes non-tangible interpersonal communication characteristics that can bind a well-oiled team together or not.

KEY TEAM MEMBERS AT A CRO

Study Team Members	Responsibilities	Characteristics of Interest
Project Manager	coordinates all timeline activities; clinical, bio-statistical and data management	big picture viewer of all the key players who is approachable, enthusiastic and knowledgeable of the study particulars with a cooperative personality to inspire each team member to do their job well and on time
Medical Monitor	answers study eligibility and ongoing medical concerns	well versed in the medical condition, therapeutic area and drug indication
Clinical Monitors	quality control checker of study data accuracy against source documents, medical charts and laboratory results	track record for being thorough in the decided mode of monitoring: 100% review or risk-based monitoring
Data Manager	DMP, DTA, database cleaning	familiar with the eCRF software with timely follow through and follow up
Bio-statistician	writes the statistical portion of the Statistical Analysis Plan (SAP) with shell Tables, Listings and Figures (TLF)	clear big picture understanding of the connection between clinical data, statistical analysis principles and oversight of statistical programmers
Statistical Programmers	program the SDTM and ADaM data sets, TLFs, and define files	(usually not at a bid defense meeting)
Medical Writer	writes the Clinical Study Report	(usually not at a bid defense meeting)
Subcontractors	fills in the gaps of a full-service CRO	previous experience with the CRO, the CRO will work with them seamlessly for the sponsor

Table 2. Key CRO study team members responsibilities and their personal and professional expertise and characteristics of interest.

STUDY CONDUCT

Effectively matching a sponsor's expectations to a CRO's abilities is a key indicator for successful project planning. It is important to ask if the CRO's biostatistician or someone he or she delegates to will be involved in a study's SAP development and in the protocol design, eCRF design, UAT of the eCRFs, edit check review, review the SDTM and ADaM data sets, final TLFs, and creation of the FDA submission ready define files for SDTM and ADaM data. This may seem trivial to the statistician but to a project's success, it is better to find problems early rather than to wait until the last minute when it may be too late.

STUDY DOCUMENTS

A study's flow of documents begins with a sponsor generated study synopsis, and study protocol that get delivered to a CRO prior to the bid-defense. The CRO awarded to a study creates the unique CRFs, the complete set of eCRFs by visit, initiates the UAT review for the eCRFs, generates edit checks, the DMP, DTAs, SAP and TLF shells, TLF outputs for database close and database lock, SDTM and ADaM data, the define files, and the CSR.

The study synopsis and protocol explains the study phase in a drug's development, rationale for the study, the study objectives, intervention, the Schedule of Assessments, inclusion and exclusion criteria and highlights statistical methods and sample size.

The eCRFs collect the study data from study subjects. Entries are by the study subject and / or a clinician at a hospital, clinic or medical research facility. A UAT checks the flow of real time responses on an eCRF. Edit checks are data logic checks run in real time and after the fact.

A DMP explains the data entry software, database structure, data flow from data entry to hard lock, coding of adverse events, coding of prior and concomitant medications, data cleaning procedures, any external vendors, role and responsibility and the frequency and method of communication between the CRO and the Sponsor regarding the same, it lists a CRO's SOPs to be followed for these processes, and data deliveries to the Sponsor.

A DTA is created to explain the procedure for data transfers from an external vendor to the CRO or the CRO to the Sponsor. It contains information about the data transfer mode, frequency, format and structure.

An SAP is similar to the protocol but includes in depth information regarding the analysis of study data. It includes the definition of baseline safety and efficacy evaluations, use of unscheduled visit data, how to handle missing data, statistical methods, TLF shells and the final deliverable define files.

The TLF outputs contain the actual study data and are usually delivered with SDTM and ADaM data sets based on their respective CDISC IGs.

The SDTM and ADaM define xml files have CDISC formats defined that need to be followed for acceptance by the FDA at the time of submission. These define files are usually delivered to the sponsor at the same time as the CSR.

A CSR is large final study document that discusses the study plan and its results, with TLFs explained and interpreted with regard to the study objectives.

STUDY OVERSIGHT

It is important to include all expectations in terms of procedures and deliverables into an agreed upon study timeline. A sponsor would be well served to then allow the CRO to execute the study and be accountable to these predetermined and agreed upon expectations. Red Flag warning signs that quality is slipping is when

1. The CRO uses template documents and data structures too closely without considering the study specific needs.
2. Sponsor's comments take more than one or two tries to get them corrected by any team member. This is a major indicator of inexperience.
3. Timelines are crunched because the project manager is not alerting team members of upcoming milestone deliverables.

DOCUMENT REVIEW BY SPONSOR'S ROLES

An effective approach to data quality by the sponsor comes from an Old Russian proverb that was said by Ronald Reagan is to 'trust but verify' the deliverables from a CRO. In order to do that the sponsor would need a minimum of one experienced staff statistician and one experienced data manager, else when it comes time for the FDA to review study data, the FDA may find it lacking and re-dos may be needed. Table 3 shows the division and overlap of responsibilities for a sponsor's study data manager and statistician.

KEY TEAM MEMBERS FOR A SPONSOR

Oversight	Data Manager	Statistician
Protocol development		√
eCRF design	√	√
UAT testing of the eCRF	√	
DMP and DTAs	√	

Oversight	Data Manager	Statistician
Edit check review	√	
SAP development		√
TLF's development	√	√
TLF outputs	√	√
SDTM and ADAM data sets review	√	
SDTM and ADAM define files review	√	
CSR	√	√

Table 3. The division and overlap of review responsibilities for a sponsor's data manager and statistician.

DATA REVIEW

The sponsor's statistician oversees the high level theoretical statistical method decisions in the SAP, the final interpretation of results in the CSR, and is a resource person for questions by the Data Manager. The sponsor's Data Manager focuses on everything that is data related: reviews the DMP, DTAs and SAP for agreement with the current DSC, checks the eCRF design matches the protocol, participates in the UAT of the eCRFs, reviews the edit checks, reviews the SAP and TLF shell designs, and sees that the final TLF outputs are in agreement with the TLF shells in the SAP, SDTM and ADaM data sets follow CDISC standards and the define files contain all that is required, and checks to see that all numbers that get transferred to the CSR are accurate. If the sponsor does not have the in house resources to oversee the CRO's work, then another option is to hire a supervising CRO that is well seasoned to check the completed work of the main CRO.

DATA REVIEW TECHNIQUES

When reviewing documents and data, it is often helpful to cross reference the information in one document with that in another to see if there is consistency. Table 4 illustrates the protocol's Schedule of Assessment's; it is a key document that can be referenced to check other documents. The SoA is a succinct summary of all study procedures by visit, day, hour, and exceptions, as applies. It is helpful to review this table side by side with the eCRF, UAT, Edit Checks, SAP, TLFs, SDTM and ADaM data sets and the CSR to check for consistency and to identify inconsistencies across these documents.

The FDA has a DSC (U.S. Department of Health and Human Services 2016a) that lists the version of key documents it currently supports and requires for an FDA submission. This is updated periodically and requesting a CRO adhere to the currently required versions will serve a Sponsor well at the time of submission by reducing the chances of a rejection due to technical conformance (U.S. Department of Health and Human Services 2017b, 2017c). Be sure that the most recently supported and required versions are written into your study documents to indicate their commitment for delivery. Include the version numbers in the protocol, the DMP, any DTAs, and the SAP.

CDISC guidelines are followed to create the SDTM and ADaM data sets in SAS® format and require a person familiar with the SAS programming language to review that these data sets in order to be FDA submission ready. The SDTM data structure needs to be checked by software that used to be called OpenCDISC Validator and is now called Pinnacle 21; the resulting data issues get listed in the SDTM define.xml file's linked document called the Study Data Reviewers Guide (SDRG). The ADaM data's define.xml file has a similar linked document called the Data Analysis Reviewer's Guide (ADRG) where the analysis algorithms get listed.

When reviewing an SDTM or ADaM define file, check that all links are working properly: the aCRF opens and when a specific page number is listed that it opens to that specific page, that it opens to the subcategory page that it says, the data sets open, and the within document links go to where they say they will. Check for correct spelling, that there are no special characters, i.e. only keyboard symbols, and no references to raw data sets (Fine, 2016).

SCHEDULE OF ASSESSMENTS

	Assessment Period							Follow-Up
	Screening	Induction Phase		Rest Phase	Challenge Phase		End of Study or Early Termination	
Study Day	**-42 to -1**	**1**	**2-7**	**8-16**	**17**	**18**	**19**	**49**

	Assessment Period							Follow-Up
	Screening	Induction Phase		Rest Phase	Challenge Phase		End of Study or Early Termination	
Study Day	**-42 to -1**	**1**	**2-7**	**8-16**	**17**	**18**	**19**	**49**
Outpatient Visit	X	X	X		X	X	X	
Telephone Contact								X
Informed Consent	X							
Inclusion/Exclusion Criteria	X							
Medical History	X							
Demographics	X							
Physical Examination	X						X	
Vital Signs including Height and Weight	X	X			X		X	
12-lead ECG	X						X	
Clinical Laboratory	X						X	
Investigational Product Administration		X	X		X			
Discharge from Clinic		X	X		X	X	X	
Concomitant Medication	X	X	X		X	X	X	X
Adverse Events	X	X	X	X[a]	X	X	X	X

a: Adverse event will only be captured via inbound telephone calls during the Rest Phase

Table 4. Sample schedule of assessments table of data captured at each study visit.

SOLVING PROBLEMS

When a Sponsor notices that a CRO is not meeting expectations, it is the Sponsor who needs to be calm and clear about the timeline, quality deliverables and recognize that work is a process of give and take of information leading up to quality deliverables. Maintaining a professional interaction with a focus on solving the problem(s) is the goal.

For example, since the Sponsor's ClinOps person is the key point of contact with a CRO, it is his or her responsibility to periodically inquire to the CRO to see if they are on target to deliver each study timeline item on the agreed date. When the content of the delivery is lacking, written comments, replies and updates are instructive for both parties. The CRO team members get to see the issues, and the Sponsor can look back at the written comments to see if they are resolved satisfactorily. When evaluating a CRO's performance it is import to differentiate between the task and the person. A person may be new and not have the necessary skills to complete a task. If that person is responsive to comments then the work will get done in a satisfactory manner. Otherwise, escalation of an issue is needed for the CRO to evaluate their options to fulfill the task effectively and efficiently. If the CRO cannot get the job done in a satisfactory manner by juggling their in house resources then the last resort option is to get the job done by a CRO that can rescue a project for a satisfactory conclusion.

CONCLUSION

This paper highlights the Sponsor's perspective for how to evaluate a CRO's data management and statistical services, the key team players and their roles, how to manage study conduct to keep it on track, how to evaluate deliverables the sponsor receives for successful study conduct and documentation for a submission ready data package.

REFERENCES

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