ABSTRACT

Global industry analysts estimated that pharmaceutical and biotechnology companies spent approximately $57 billion on R & D in 2005, out of which an estimated $14 billion was used for the outsourcing services offered by the CRO industry. This figure is expected to increase further with the broadening of the spectrum of services outsourced to cover the entire value chain. As the outsourced services to India move up the value chain to cover phase 1/2 trials, the total contracts value may go up to $20 billion by 2010 (Wikipedia/Contract_research_organization). With important analysis, including pivotal Phase III trials, integrated summaries of safety (ISS) and integrated summaries of efficacy (ISE), being programmed by external vendors, the need for effective relationships is critical. In this paper, we discuss key points to building an effective relationship with a CRO, including communication, timelines, programming requirements, Statistical Analysis Plan (SAP) and scope management.

INTRODUCTION

With the increased use of CROs, the sponsor Statistical Programming Manager/Statistical Programming Lead role may change/expand to include managing the timelines, productivity and quality of a vendor’s programming. While CROs introduce additional management concerns, such as scope, many of the strategies that are applied in managing internal projects can be effectively used in managing outsourced projects. The concepts discussed in this paper are meant to assist both the sponsor and the CRO in building effective working relationships.

COMMUNICATION

A communication plan is an important tool in managing the relationship between the sponsor and the vendor. Without a document detailing communication flow and tools, both the sponsor and vendor can be unclear regarding communication expectations. Details of the communication plan include the following:

1) Lead team members in both organizations with contact information (Examples of lead team members are the Biostatisticians, Programmer Managers, Lead Programmer, Project Manager). Specifically, indicate the primary contact within each organization.
   a. If the CRO needs to communicate with any organization other than the sponsor, this contact information along with expected communications should be documented.
2) The information that needs to communicated. While it may seem obvious, timeline and lead resource changes within both organizations should be communicated, and unfortunately, these details are not always exchanged. Other types of information include status reports, timeline management responsibility, and vacation schedules.
3) Meeting requirements including the frequency, the team member(s) responsible for scheduling, and the team member(s) responsible for creating agendas and writing minutes. Any approval process for agenda and minutes should be specified.
4) An escalation plan within both organizations for issue resolution. Sponsor and the CRO should use escalations steps as needed; however, team members should make every effort to resolve a problem prior to escalating.
5) The acceptable communication media (email, secure FTP site, Webportals) for the various information exchanges.

While the communication plan will guide both organizations, the team members are responsible for providing important information. Delaying critical information, such as possible scope or staffing changes may create project delays.

TIMELINES/AD HOC REQUESTS

Timelines are a critical component of any project. While managing a project schedule with an internal team is at times challenging, the complexity seems to grow when working with an external vendor. There are several steps that can be implemented to ensure a well designed timeline.
1) Create a mutually agreed upon timeline for delivering analysis items. Ideally, both organizations are willing to compromise in developing the schedule.

2) Include all of the distinct analysis, INDs, DSMBs, dry runs, interim and final analysis, and consider all of the possible tasks, deliveries to and from the sponsor and any milestones. Some suggestions include the following:
   a. Sponsor review and approval of analysis file specifications.
   b. Sponsor independent validation of analysis datasets and tables, listings and graphs.
   c. Table, Listing, Graph (TLG) delivery. If batches (a subset of the TLGs) are being delivered, each delivery date should be included on the timeline.
   d. TLG feedback from sponsor. The CRO may require consolidated sponsor feedback as the sponsor can more readily resolve internal disagreements regarding the TLGs. If consolidated feedback is needed, this should be clearly documented on the timeline.

   Sufficient time should be allowed for these activities, and if iterative cycles are anticipated, they should be included on the timeline.

3) Within both organizations, share the timeline with all the team members and other personnel as required. The leads need to ensure that their teams know and understand the schedule.

4) Adhere to the timeline. If timeline changes are needed, discuss with the entire (CRO and sponsor) team and update the timeline. (The communication plan specifies who is maintaining the timeline.)

A frequent issue between CROs and sponsors is the scheduling of ad hoc requests. Conflict may be avoided by informing the CRO as early as possible of additional analysis. While the details may not yet be available, a general idea could allow the CRO to start considering scheduling and resources. To further facilitate implementing ad hoc requests, an appropriate mock up and specification should be developed between the sponsor and the CRO. Clarity will definitely assist the CRO in more readily producing the additional analysis. Finally, just as with the overall timeline, discuss a mutually agreeable timeline and be willing to negotiate.

Keep in mind, that a timeline is not simply a static schedule. Not only do timelines change, they have dependencies upon other parts of the schedule. While the details of the analysis timelines are of great importance to the Biostatistics and Programming Team, the overall timeline impacts the analysis team’s specific responsibilities. Team members should be well informed of the key milestone dates across the project. Also, within each organization, CRO and sponsor, the project timeline is likely only one of many timelines being managed. These multiple timelines may impact one another as well as specific team members. Given the multiple projects that impact all of us, friendly gentle reminders can be beneficial. For example, in a team meeting, the sponsor might mention that they are looking forward to receiving the TLGs next Tuesday on the 15th, and the CRO, when issuing TLGs, might remind the sponsor that the consolidated feedback is expected on the 28th. Reminders should be used carefully as excessive use could lead to tension in the relationship; however, both organizations should appreciate and understand that specific target dates might need to be reinforced.

STATISTICAL ANALYSIS PLAN AND PROGRAMMING REQUIREMENTS

Prospectively discussing any specific requirements prior to SAP development and programming, should lead to a more effective analysis implementation. The items below may lead to complications during analysis unless they are clearly defined in the SAP or supporting documentation, and the CRO and sponsor together can ensure that these details are discussed at an early stage.

1) SAS Version
   a. While moving programs from a “lower” version of SAS to a “higher” version of SAS is generally not problematic, the opposite could be quite time consuming. The “lower” version of SAS may not support certain features used in the “higher” version of SAS. The SAS version should be specific in the SAP.

2) Platform requirements
   a. While the CRO need not use the same platform as the sponsor, the CRO may need to be mindful of sponsor platform requirements. Certain code may be developed for “dual-platform” use; however, these strategies are more easily employed at programming start up.

3) Directory structure needs
   a. A misunderstanding regarding directory structures may not prove as problematic; however, any unnecessary re-work is always advisable.

4) Use of sponsor programs
   a. Expectations regarding the use of sponsor code should be addressed as early as the proposal stage. Critical issues to consider are the current validation status of the program and the available documentation and technical support.

5) Sponsor independent validation of programming
a. Prospectively discussing sponsor independent validation of programming will potentially allow for more efficient strategies. The sponsor and CRO can consider certain automation strategies as well as a reconciliation process.

6) TLG layout requirements including font size, font type, margin requirements and final deliverable format (PDF, Word, RTF)
   a. While certainly problematic in the programming stage, this information is very beneficial in the SAP, mock-up development period. The sponsor is more likely to receive the desired product, if the mocks reflect the sponsor needs. Both the CRO and sponsor should play an active role in avoiding TLG re-programming due to layout issues.

7) Any standard analysis derivations, assumptions being used within the investigational drug and/or indication (for example, imputation start date rules and or treatment emergent definition).
   a. If the CRO is writing the SAP, it can benefit from knowing any existing analysis derivations and assumptions. The CRO can integrate these rules into SAP without spending time investigating, developing possible strategies to discuss with sponsor. The CRO and the sponsor share in identifying any existing analysis conventions.

SCOPE

The CRO obviously has a vested interested in managing the project scope; however, the sponsor team also benefits from understanding the contract scope. Some of the issues that arise during the course of a project are misunderstandings regarding responsibilities and expectations including INDs, dry runs, and TLG volume as well as the necessary steps to begin out of scope work. At project start, both organizations are well served by a brief joint review of the scope as well as processes for expanding.

CONCLUSION

Effective relationships between sponsors and CROs can readily be developed. By following good communication, timeline, SAP/Programming and scope management practices, both organizations will benefit from a high quality, on time product.

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