



## Extending Compliance to Sponsor-CRO Partnerships

Although outsourcing arrangements have typically been of mutual benefit to both sponsors and clinical research organizations (CROs), improvements in the collaborative process are necessary for both parties to meet the demands of the market.

**R**elationships between sponsors and clinical research organizations (CROs) have evolved from tactical interactions that provide staffing or limited services required for study support, toward a more strategic, collaborative relationship that benefits both parties. Increased regulatory requirements, site placement in global locations, and the need for sponsors to improve cost and efficiency opportunities in development operations at a time of significant downsizing throughout the industry are examples of why outsourcing strategies in clinical trials are being aggressively pursued by sponsors.<sup>1-3</sup>

CROs and sponsors have also benefitted through such partnerships by extending service offerings to areas outside traditional development tasks into research-oriented services and partnerships that contractually support shared risk-reward collaborations and financial incentives for successfully commercialized products. More than 65% of sponsors report using CROs for clinical trials, and indicate that they expect growth in outsourcing strategies used in support of protocol, compound, and product pipelines to continue.<sup>4</sup>

### Shared-Ownership Operational Models

In defining the structure and responsibilities in the shared operational relationship, both sponsors and CROs can be challenged not only by the daily operational and logistical challenges, but also by the requirements that govern and guide industry. Such challenges have also caught the attention of the U.S. Food and Drug Administration (FDA), which issued guidance specifying that, although trial-related duties and functions may be transferred by the sponsor to a CRO, the sponsor will ultimately remain responsible for the quality and integrity of the trial data<sup>5,6</sup> associated with the outsourced activities. In assuming these responsibilities, the CRO should be prepared to implement quality assurance control efforts in support of regulatory requirements and successful execution of assigned activities.

The FDA suggests that designation of responsibilities and assignments are to be described in writing to ensure clear understanding of which party is participating in which activity and responsible for which deliverables.<sup>6</sup> Although this requirement is usually addressed in the service agreement between the sponsor and CRO, the details associated with such assignments can at times be vague and incomplete, setting both parties up for potential consequences from a regulatory and competitive stand-

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point. Such guidance was issued with the intent of curtailing the multiple instances of noncompliance reported by the FDA around the shared operational nature of sponsor/CRO collaborations.<sup>7</sup> CROs have been found in violation of regulations supporting delivery of specific services, and sponsors in violation of CRO oversight. In a time of declining revenues and increased costs, such occurrences can significantly impact the ability of both parties to fulfill strategic objectives and corporate initiatives critical to corporate success.

In order to adhere to regulatory requirements, sponsors and CROs have an array of corporate policies and procedures specific to clinical trial conduct, addressing such key activities as site initiation, drug accountability, and investigator conflict of interest. These policies and procedures also serve to demonstrate transparency of business practices that address quality requirements associated with corporate goals and objectives.

Adherence to internal processes and procedures pertaining to clinical trials supports efforts to demonstrate corporate-level compliance with applicable regulations, and authenticates the accuracy and completeness of corporate financial statements and disclosures. Although these initiatives act to support corporate and contractual

requirements associated with compliance, quality, and oversight, the level of detail provided may not address specific and granular information required to independently support the needs of the shared operation structure in the sponsor/CRO collaboration, or the individual requirements of complex, unique studies.

### **The Activity-Based Approach**

Efforts to improve the shared operational relationship between sponsors and CROs present several challenges regarding transparency, oversight, and responsibilities. Depth and descriptive detail around planned work, required resources, and associated costs are consistent themes in identifying areas for improvement. Sponsors report that CROs can, at times, demonstrate a lack of transparency around billing, poor communication regarding activity status and issues, and an inconsistent commitment to project deliverables and success; CROs indicate that there is significant opportunity for improvement in defining the extent of work to be done, and to communicate effectively around work detail.<sup>8,9</sup> A methodology that allows improvements in collaboration, communication, and integrated operational strategy must be pursued by both parties to ensure that improvements are recognized in support of the success of the shared operational model.<sup>10</sup>

An activity-based approach—also known as a “bottom-up” or “project management” approach—to clinical trial planning is one method that can be utilized in the shared operational model to ensure that work is defined at the level at which it occurs, capturing all activities required in support of a study prior to its initiation. By using this method to identify all tasks required for successful study completion, many issues reported as challenges in the shared operations relationship can be addressed.<sup>9</sup>

Work is identified at the task level, and then organized into related groups

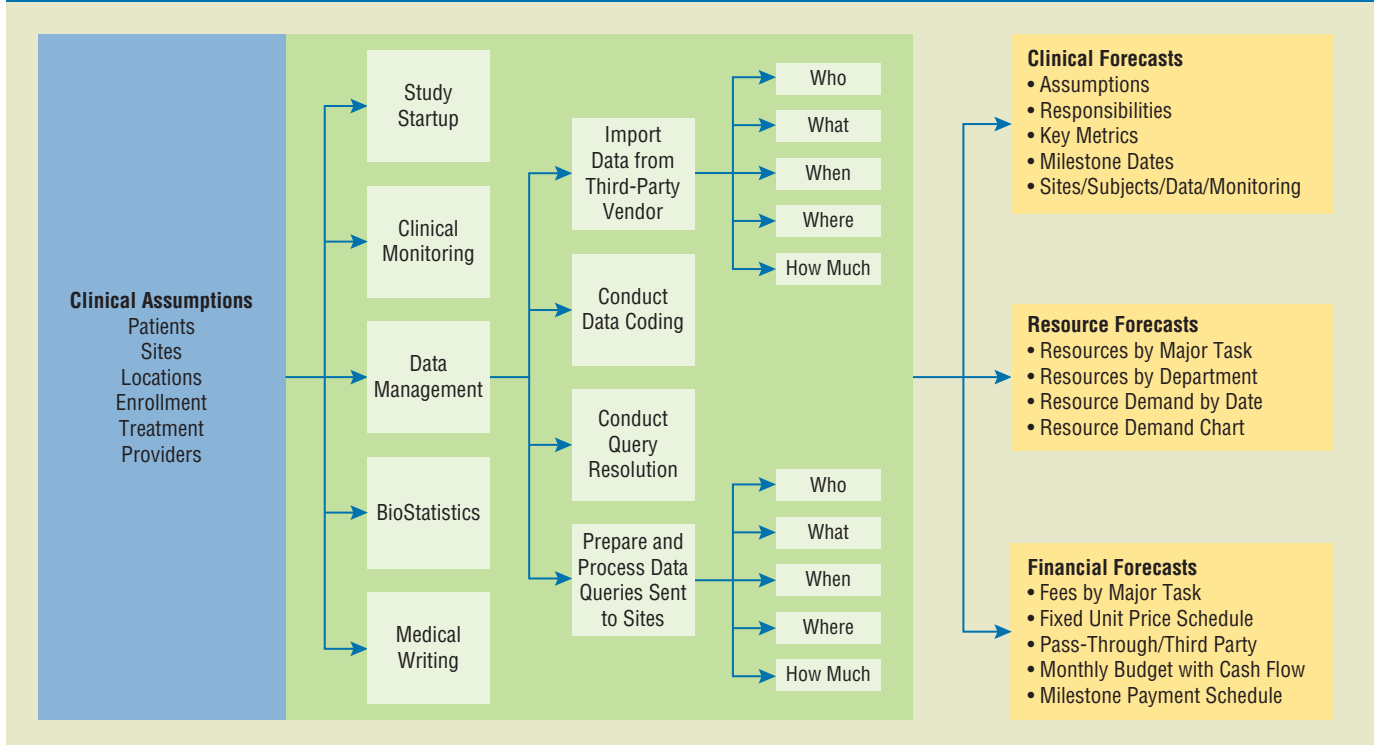
of tasks forming general activities (Figure 1). From that effort, resource needs are assigned; plan interdependencies around critical events are identified; and study milestone dates and budget forecasts are generated. This information acts as a foundation for communication and performance measurement throughout the study lifecycle. Additional mitigation strategies can then be developed to extend traditional, sponsor-based controls to the CRO in support of study and business requirements.

Efforts to establish an activity-based plan are usually started as early as the availability of the protocol synopsis, and continue throughout the study planning process. The plan is collaboratively developed and finalized with input from all members of the study team, including representatives from the project management, clinical operations, regulatory affairs, data management, business operations, and outsourcing units.

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Request-for-proposal (RFP) documentation, including plan tasks and milestones, contracts, and the protocol, are the foundation used to build the shared operating model required in sponsor/CRO collaborations. Care must be taken to ensure that the RFP process utilizes input and review of key members of the sponsor study team. This effort should be reflected in the delivery of a contract that supports study objectives, regulatory requirements,

**Figure 1** Activity-Based Planning



and the financial and business objectives of the sponsor and CRO. The efforts and deliverables of each party, the expectations around performance-tracking methodology, and the quality requirements of the data collected are areas where detail may be lacking and require additional oversight, explanation, and continuing discussions to ensure study objectives and business requirements are met.

### Controls

Project management activities prior to enrolling the first patient involve planning efforts supporting quality assurance, team meetings, status reporting, and logistics, which will form the basis of successful study operations. The activity-based planning approach accounts for each activity to be completed during the study, capturing detailed work requirements and associated resource needs estimated against each task. This comprehensive list of tasks and associated units for resource and cost assessments

can serve as a standardized “bid grid” used in the RFP process.

Other helpful information that can be generated from the detailed plan in support of the RFP process includes key assumptions, a responsibilities matrix, and milestone dates. Once the contract has been awarded, the plan can be used as an effective reference tool to designate responsible parties for tasks performed in specific study locations,

particularly if responsibilities differ in different locations (Table 1).

In some sponsor organizations, the process for managing the shared operational relationship sits within the outsourcing group. Outsourcing can specifically benefit from using activity-based planning in several ways. First, outsourcing can easily generate plan scenarios that reflect resource needs and cost implications

**Table 1** Responsibilities for Tasks Associated with Project Management

Project Management Week Prior to First Subject in	Bulgaria	France
Plan study specifics	Major CRO	Major CRO
Plan data coordination activities	Major CRO	Major CRO
Plan administrative support functions and interact with third party vendors	Major CRO	Major CRO
Plan information support functions	Major CRO	Major CRO
Plan quality assurance activities	Sponsor	Sponsor
Manage project personnel and assignments	Major CRO	Major CRO
Manage CRO/sponsor interactions	Major CRO	Major CRO
Manage/attend weekly operations meetings	Major CRO	Sponsor
Manage data coordination activities	Major CRO	Major CRO
Assess deviations from plan, identify out-of-scope activity, address with sponsor	Major CRO	Major CRO

that support a variety of outsourcing methods (e.g., fully outsourced, functional outsourcing), and compare those scenarios to identify the best plan for the sponsor business and study requirements.

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Activity-based planning also allows improved accuracy of budget forecasting for studies resourced using preferred CRO providers. In those instances, activity-based plans can be generated using prenegotiated billing rates to specifically calculate identified resourcing needs. Finally, activity-based planning can assist with quicker contract closure, as all parties understand plan activities by which bids are developed and evaluated, and streamline the change order process by allowing quick reforecasting to reflect a change in total number of patients, increased number of case report form (CRF) pages, or additional monitoring visits.

In order to recognize these benefits, outsourcing groups managing CROs must frequently interact with, and solicit feedback from, study team representatives in order to support the collaborative, integrated approach that is required for activity-based planning to succeed.<sup>10</sup>

### A Scenario for Controlling Risks

A study team has selected 25 sites in five countries to support an upcoming protocol. An activity-based study plan is generated, identifying all tasks required for study activities and related

interdependencies, and the required resources and materials to support each task. The study team is therefore able to forecast study costs based on the groups of required tasks and the associated resources required for task and study completion (Table 2). In doing so, both the sponsor and CRO now have a detailed record of specific tasks that will need to be performed, the resources performing the tasks, the estimated hours the tasks will require to be completed, and the associated costs to achieve the deliverable in support of study objectives.

As all of the designated tasks associated with site approval are assigned to CRO resources, the sponsor has asked the CRO to review the status of each task until all sites are initiated during routine study team meetings, as described by the standard operating procedure (SOP) for the sponsor's study communication plan. Both parties review the SOP, and agree that additional information regarding the task of contract negotiation was required: In several study locations, the CRO would be required to negotiate agreements with the hospital, pharmacy, and laboratories used by sites, which both parties agree could delay site initiation and compromise downstream study activities.

The CRO has agreed to provide a weekly update during site activation, detailing the status of specific agreements for each site with the communication plan updates. This allows the sponsor greater transparency into site initiation activity progress, and provides the CRO with a method to proactively identify, describe, and escalate issues potentially impacting site activation and future activities dependent upon site activation completion, mitigating impact on projected timelines and study budget.

### Controls Supporting Patient Enrollment

Patient enrollment drives many key activities of study operations, including monitoring visits, CRF generation and queries, drug distribution, and project management. If enrollment forecasts change over the course of the study, such risks are introduced to future tasks as delayed data analysis; increased costs associated with site management, project management, and monitoring; extended resource efforts; and increased potential for study drug expiry/availability problems. By allowing for changes in such key variables as enrollment period and the anticipated enrollment curve, detailed study plans

**Table 2** Site Approval Tasks, Hours, Costs, and Resources

Site Approved	Hours	Cost	Site Approved	Hours
Distribute protocol	11.2	1,711	CR01 - Clinical Research Associate	709
Negotiate site contract	270.5	53,538	CR02 - Senior Clinical Research Associate	0
Provide IRB submission support	178.9	27,269	CR05 - Senior Director, Clinical/Therapeutic	68
Collect regulatory documents	428.2	55,207	CR07 - Project Administrative Assistant	171
Collect miscellaneous study preparation documents	146.2	22,245	RG01 - Regulatory Submissions Specialist	162
Set up regulatory files at the site and hold training meetings	129.4	19,544	RG02 - Regulatory Submissions Manager	99
Request and approve drug shipment	45.0	6,423	RG03 - Director Regulatory Affairs	1
<b>TOTAL</b>	<b>1209.4</b>	<b>185,936</b>	<b>TOTAL</b>	<b>1209</b>

enable quick adjustments supporting a variety of possible scenarios. In developing several scenario plans to compare and consider based on projected enrollment curves, study teams can select the plan that best fits their needs in terms of schedule, resourcing, and costs.

As an example of this concept, a study was planned that anticipated enrollment of 175 patients during a 78-week period, reflecting a bell curve enrollment distribution. The sponsor intended to outsource monitoring services, and was in the process of evaluating RFP bids from several CROs supporting an estimated average of 230 monitoring hours per week, as determined using the detailed study plan. During this time, sponsor executive leadership requested that the study team shorten the specified enrollment period for the study to 52 weeks, in support of an expedited approval strategy. The study team quickly generated a revised plan by adjusting the designated enrollment

period and monitoring visit frequency specified in the monitoring plan SOP.

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In this manner, the team was able to generate a new plan scenario that provided adjusted resource requirement needs and associated costs that represented the shortened enrollment period and its impact to the monitoring visit schedule. The sponsor used this infor-

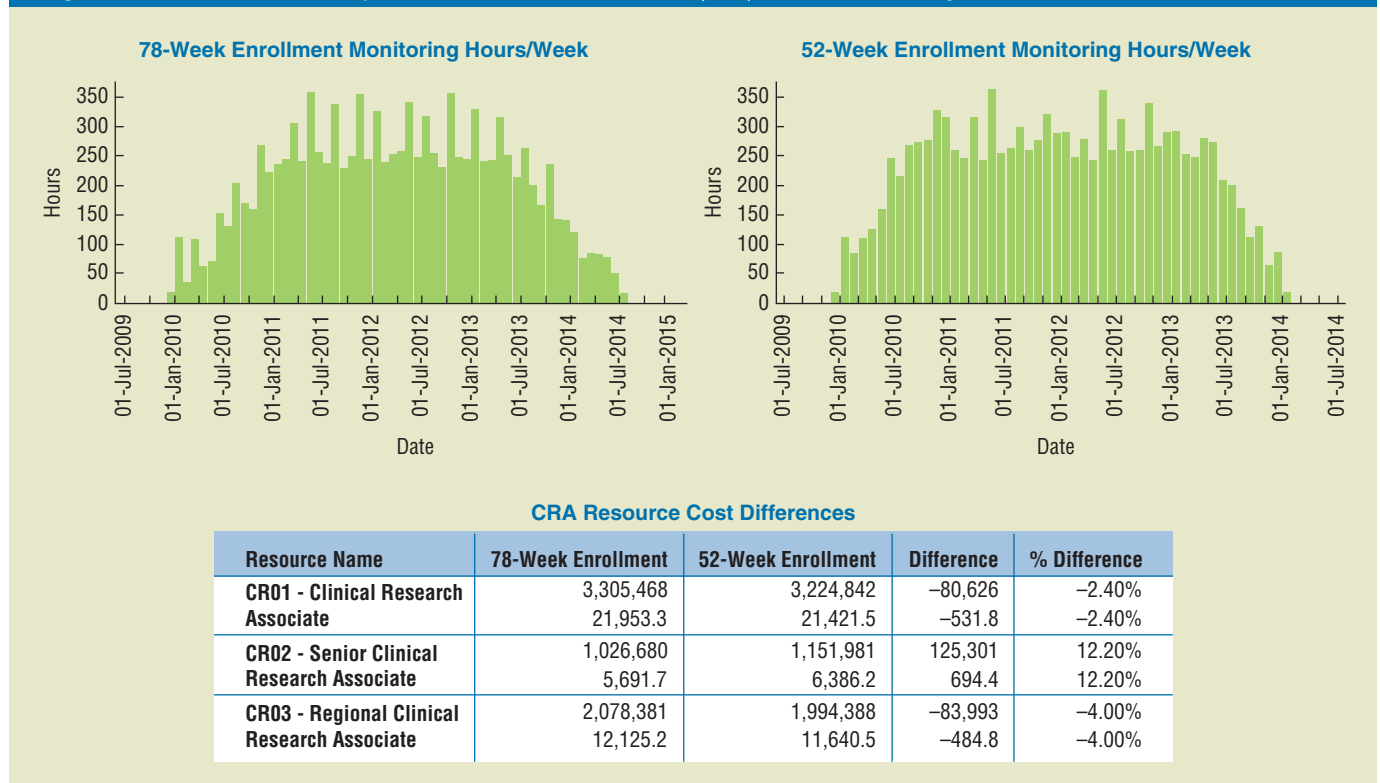
mation to request adjusted bids to the previously provided RFP, in support of the revised scenario plan that required an average of 247 monitoring hours per week. Using that information, both parties compared the initial scenario against the recalculated costs for monitoring generated by the new scenario plan to determine feasibility, as well as cost implications for enrollment period adjustment (Figure 2).

In assessing the scenario plans and the impacts to resourcing and budget estimates, the sponsor and CRO were able to proactively develop a resourcing plan and budget that supported either the 52- or 78-week enrollment scenario, and to articulate how those adjustments affected cost and resource requirements for the study if the enrollment period was shortened as requested.

## Summary

Outsourcing functions or service groups associated with clinical trial operations

**Figure 2** Enrollment Schedule Impact to Clinical Research Associate (CRA) Resources and Budget



meet a variety of needs associated with a changing market, and present significant opportunities for growth and efficiencies to both sponsors and CROs. The manner in which shared operational study plans supported by sponsor/CRO collaborations are executed requires improvements that focus on transparency and delineation of responsibilities in order to mitigate risks and impact to study success. A variety of existing procedures, legal documents, and methods guide industry, and utilization of these collective processes must be incorporated into the study planning process (Figure 3).

An activity-based planning approach allows sponsor/CRO collaborations to understand the work required to plan study resourcing, timelines, and budgets. An extension of this process involves utilization of existing policies and procedures that support regulatory, business operations, and oversight initiatives to both sides of the partnership, so that all parties are collectively engaged toward common goals and requirements. Additional controls specific to study objectives that detail patient enrollment, resource availability, and detailed communication further strengthen the opportunities presented

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by the shared operational model, and should be pursued as a method of engagement from the RFP process throughout the study lifecycle.

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**Figure 3** Controls to be Used in Outsourced Clinical Trials

