Financial Issues Related To Outsourcing

A Contract Research Organization Perspective

Donald L. Crone

Director
Department of Clinical Data Management and Statistical Services
Biotechnical Services, Inc.

What You Will Learn

- The importance of the Request For Proposal
- The Important parts of the proposal
- Contract mechanisms for accounting for in-study changes
- Logistics of study scope changes to an executed contract

The Main Points

- Understand what the sponsor is wanting you to do for them
- Price your services so you can meet or exceed the sponsor's expectations and you can stay in business
- Do your very best for your sponsor and your company

The Request For Proposal (RFP)

- The RFP initiates business discussion
- The RFP defines the sponsor-defined tasks on which you bid
- The more details included in the RFP, the more accurate the bid will be

An Example of an RFP with few details

- Case report form generation and printing
- Database setup and validation
- Clinical data receipt from sites and external sources

RFP with few details

- Data entry into databases
- Data analyses of cleaned data
- Data transfer to sponsor

Details—The More the Better
RFP with plenty of details

- Project Management
- Study Management
- Monitoring
- Medical Management
- Data Management
- Quality Control
- Statistics
- Report Writing
- Audits
- Printing
- Shipping
- Quality Assurance

Then More Detail…

Project Management

- Kick-off Meeting (per meeting) 0
- Project Team Training (per session) 0
- Project Management (Per month) 0
- CRO-Sponsor Meetings (per meeting) 0
- CRO Project Team Meetings(per meeting) 0
- Other 0

Project Management Sub-total: 0

Then Definitions…

Project Kick-off Meeting

- A one-day meeting will be held at a venue to be agreed with sponsor and will include sponsor and CRO representatives from each project area.
- The project manager and Study manager should agree to a date and venue and liaise with their teams, organizing attendance and conduct of the meeting.
- The Study Manager will chair the meeting.

More Definitions...

Project Kick-off Meeting... All attendees should...

- **Prepare for the meeting by familiarizing themselves with the study documentation**
- **Participate in the Kick-off study meeting discussion, assessment, and planning for each of the outsourced activities**
- **Agree on dates and responsibilities for activities that will contribute to the Milestone Payment Schedule in the RFP. Relevant team members should address action items**
- **PM will provide StM with the first draft minutes. sponsor team members will review and comment. CRO will revise the minutes and circulate to all CRO and sponsor team members**

Then More Definitions…

Project Kick-off Meeting continued

- If the CRO is arranging the meeting facility, costs for any meeting rooms should be agreed with sponsor, and charged as a pass-through cost
- CRO will provide project-specific training for CRO and on an ongoing basis as necessary. This training is designed to ensure all team members are familiar with the outsourcing requirements and their role within the team
- Items discussed at these meetings will include, but will not be limited to…

How To Respond to the RFP

- After reviewing the RFP and other study related materials:
  - Ask specific questions - in writing
  - Ask requesting sponsor for their answers - in writing
  - Make assumptions and list each one in detail in the proposal

From RFP to Proposal

- Spread sheets
- Unit cost times number of units
- Assumptions

Database Setup and Validation

- Includes developing and validation of :
- Database tables for all CRFs and Labs
- Annotating CRFs with data field names
- Input screens to capture all CRF data
- Compare programs
- Compare edit screens
- Production edit screens

Database Setup and Validation

- Audit trail screen
- CRF Tracking system and database
- Data Clarification Form screens and database
- Edits and screening queries
- Programs to convert lab data to CRO format

Database Setup and Validation

- Setup coding program to code concomitant meds and procedures
- Setup coding program to code AE's
- Programs to convert study data to sponsor format
- Programs to report to FDA and IRB
- Providing sponsor read-only access to study database tables

Database Setup and Validation

- Writing Medical/Data Review Guidelines
- Writing Keying Guidelines

The Proposal

- **Capabilities**

Experience

- Short job descriptions of key personnel
- CVs of key personnel
- Generic descriptions of other clinical studies

Study Plan

How we propose to have all processes in place by the time they are needed

- CRFs
- Databases (tracking, subject, laboratory)
- Medical and Data Review Guidelines
- Input screens
- DCF systems
- Encoding dictionaries/systems

Project Management

Describe the process we will use to handle the day to day responsibilities of processing the data

- Receiving the data
- Logging it in
- Reviewing the data
- Entering data into database
- Generating DCFs

Communication with Sponsor

- Teleconferences
- Email
- Progress Reports

Standard Payment Terms

- Outline milestones
- Define associated payments

Duties

- Activities Performed by Sponsor
- The following list specifies the tasks for which the Sponsor assumes primary responsibility:

Sponsor Project Administration/Management

- Develop Protocol
- Establish list of assigned project personnel, name, title, etc.
- Review Standard Operating Procedures
- Develop Project Specific Standard Operating Procedures
- Produce study bulletin

Sponsor Project Administration/Management
continued

- Develop a list of Investigators
- Develop Investigator Budget
- Negotiate Investigator Budgets
- Submit Investigators to IND
- Create Randomization Schedule and site specific allocation schedule
- Establish project timeline schedule (MS Timelines)

Sponsor
Study Materials

- Contract for Manufacture of Study Drug(s)
- Contract for Package and Label of Study Drug(s)
- Store Study Drug(s) / Ship Clinical Supplies to sites
- Provide sites with Drug dispensing Logs
- Design Case Report Forms
- Prepare instructions for investigators to accurately complete CRFs
- Design source document worksheets for site use

Sponsor
Study Conduct Documentation

- Review and approve Routine Monitoring Guidelines
- Review and approve Medical Review Guidelines
- Train medical review personnel on Medical Review Guidelines*
- Review and approve project specific SOPs and guidelines

Sponsor
Study Start-Up

- Conduct Multi-Investigator Meeting
- Develop and present Data portion of Investigator Meeting(s)
- Develop and present Clinical portion of Investigator Meeting(s)
- Develop and present Regulatory portion of Investigator Meeting(s)
- Coordinate Selection of Central IRB (if applicable)
- Prepare and Distribute Regulatory Packets

Sponsor
Study Conduct

- Maintain Secure File of Regulatory Documents
- Maintain copy of Regulatory Documents and Correspondence for use in monitoring
- Conduct Monitoring Visits (at intervals of 6-8 weeks), generate written Monitoring Reports and forward to Sponsor upon completion
- Generate written Monitoring Reports Summaries to each investigator after each site visit
- Conduct Co-Monitoring Visits as needed
- Maintain contact with Study Sites as needed

Sponsor System Setup

- Review and approve annotated CRF
- Review and approve database and validation of database
- Review and approve detailed specifications for edit checks
- Review and approve validation for edit checks
- Define Worksheet fields to be coded
- Provide CRO with Dictionaries and quarterly updates for coding

Sponsor
Study Closeout

- Conduct Study Closeout Site Visits and Prepare Visit Reports
- Perform Drug Accountability Audits
- Dispose of Unused Clinical Supplies (e.g., CRFs, worksheets, etc.)
- Coordinate return of Unused Drug Supply to Sponsor

Sponsor
Study Closeout
continued

- Verify return of Unused Clinical Drug Supply to Sponsor
- Provide required documentation of site closure
- Conduct GCP Field Audits as necessary and provide written report
- Review Final Coding

Services Provided by CRO

The following list specifies the tasks for which the CRO assumes primary responsibility

An asterisk (*) denotes tasks for which the CRO will provide support to the Sponsor.

CRO Project Administration/Management

- Participate in project teleconferences and face to face meetings as necessary (e.g., biweekly teleconferences and scheduled face to face meetings)
- Produce meeting minutes and agendas, minutes to be provided within 3 business days
- Produce data management section of study bulletin(s)

CRO
Study Conduct Documentation

- Write Routine Monitoring Guidelines
- Update Routine Monitoring Guidelines with Sponsor approval
- Train monitoring personnel on Routine Monitoring Guidelines
- Write Medical Review Guidelines
- Train medical review personnel on Medical Review Guidelines
- Update Medical Review Guidelines with Sponsor approval
- Develop project specific SOPs and guidelines
- Update SOPs and guidelines with Sponsor approval

CRO
Study Startup

- Establish secure filing system for CRF (original and working copies) and DCFs
- Develop Patient tracking system to monitor enrollment/drops and provide monthly reports
- Develop Project tracking system for CRF processing and provide reports as requested

CRO
Study Conduct

- Report Serious Adverse Events (SAE) to Sponsor*
- Conduct 100% reconciliation of database AEs with Sponsor SAE database*
- Provide data and reports including tables and text as required for safety reports (e.g., Safety Update, IND Annual Updates) as required to meet regulatory requirements*

CRO
System Setup

- Provide annotated CRF
- Develop database and validation plan
- Provide detailed specifications for edit checks
- Program, validate and provide documentation for edit checks
- Establish validated autoencoding capability

CRO
Study Closeout

- Review final coding
- Final edit check run and review
- Run Patient Data Listings and perform 100% manual comparison between CRF/DCF and database for specified fields (e.g., AEs and primary endpoints)
- Verify closeout of all DCFs

List of Fees for Services

- **Variable Costs:**
  - Data Entry
  - Data Management Review of CRFs/Lab
  - Medical Review of CRFs/Lab Reports
  - Algorithm for Collapsing AEs – Programming, Validation, Collapsing
  - Summary Table Definition, Programming, and Validation
  - Production of Summary Tables (draft, interim, and final)
  - Data Listings Definition, Programming, and Validation per Listing

Fixed Costs

- Cost items that don't change depending on the number of subjects enrolled in the study
- Examples:
  - Database Design
  - Write/update Project Specific SOPs
  - Data Management Plan (DMP) – write/train/update

Pass-Through Costs

- Costs which the CRO incurs in the course of doing the sponsor's business
- Example:
  - Investigator meeting arrangements
  - Facility Rental/Equipment
  - CRO staff travel/accommodation
  - Incidental expenses

The Good News

- You are selected to provide services for sponsor's study
- Do the contract

The Contract

- Terms of Agreement
- Scope of project
- Time schedule
- Transfer of obligations
- Reporting Requirements
- Compensation

Parts of the Contract

- Publications
- Adverse Experience Reporting
- Confidentially
- Indemnity
- Contacts
- Property Ownership
- Changes in scope of studies

Changes in Scope of Studies

- Include provisions for making adjustments to the basics.
- Example:
  - Number of subjects
  - Number of CRFs
  - Number of listings,
  - How to handle new tasks assigned to CRO

Work Orders

- Changes to the scope of work.
- After the contract is signed
- New or additional requirements for the CRO that were not in the original contract.

REQUEST FOR CHANGE

- **Example:**
  - **The number of listings in the contract was reduced from 20 to 19; the resulting impact on the contract value is a decrease of $950.00.**
  - **The number of tables in the contract was increased from 20 to 23; the resulting impact on the contract value is an increase of $3,900.**

Contact Information

Don Crone

Director of Clinical and Data Management Services

Booth 645

Biotechnical Services, Inc.

4610 West Commercial Drive

North Little Rock, AR 72116

Phone: (501) 758-6290 extension 127

FAX: (501) 753-5963

Email: dcrone@biotechnicalservices.com