

Developing and Managing CRO Relationships

December 2009

LESSONS LEARNED



THE STORY BEGINS

- ✘ ElvinsRx is a reasonably well-funded biotechnology company developing an exciting therapeutic for cancer. The underlying technology is platform-based, so there are opportunities for therapeutics to treat a number of cancers. The company's lead product, E-103, is about to enter a Phase I clinical trial in kidney cancer. The trial is a critical test, not only of E-103, but of the platform as a whole.
 - + ElvinsRx recently hired a CMO from Big Pharma, but has no other clinical staff yet. The CMO plans retain a CRO to manage the Phase I trial. You head up the regulatory/quality function for ElvinsRx, and the CEO has asked to to take the lead in sourcing a CRO and negotiating the master services agreement. You worked for the CEO at another company. She recruited you to ElvinsRx and trusts your judgment and prior experience. Like all CEOs of small biotechs, your CEO wants the trial started and completed as soon as possible. She's also cost conscious.
 - + What are some of the important things to think about before starting this assignment?

THE STORY BEGINS, CON'T

- ✘ Is there more that could be done internally to prepare?
- ✘ What clinical trial tasks could be managed internally?
- ✘ Does an RFP make sense?
 - + Means for identifying needs and issues
 - + Creates competition and increases negotiating leverage
 - + Expedite MSA
 - + Time constraints

BID DEFENSE

✘ Prepare

- + Best opportunity to learn what you need to know to understand the proposal and what's not in the proposal
- + Attended by CRO's proposed team
- + Develop questions in advance
- + Vet qualifications and test communication style of each participant

BID DEFENSE, CON'T

- ✘ Delve into internal workings
 - + Caseload per project manager and CRA
 - + Project manager responsibilities
 - + Internal communication methods
 - + Use of subcontractors, affiliates and independent contractors
 - + SAE response process
- ✘ Understand bid and assumptions
- ✘ Understand proposed payment terms and insurance requirements
- ✘ Understand what else you will need to pay for, such as software

THE START-UP AGREEMENT

- ✘ You've selected a CRO, NW. The NW business development lead has sent you a copy of NW's standard start-up agreement and master services agreement. He urges ElvinsRx to sign the start up agreement so that NW can draft the protocol and begin other tasks necessary to commencing the clinical trial.

- ✘ Is this a good idea?

- ✘ What should be in the start up agreement anyway?
 - + Clear definition of tasks and responsibilities
 - + Specific budget
 - + Specific timelines
 - + Short term
 - + Express statement that MSA will control from inception of start up agreement

THE MASTER SERVICES AGREEMENT

- ✘ The Start Up Agreement is done and now its time to negotiate the master services agreement. Nationwide sends you a copy of its standard template. It seems pretty general and light on detail to you.
- ✘ What types of provisions will you want to make sure the agreement includes?

THE MASTER SERVICES AGREEMENT, CON'T

- ✘ Who will do what?
 - + Detailed work order
 - + Accuracy of assumptions

- ✘ What if changes are necessary?
 - + Advance notice
 - + Justification
 - + Budget revision
 - + Written agreement

THE MASTER SERVICES AGREEMENT, CON'T

- × Who will do the work?
 - + Subcontractors and other independent contractors
 - × Notice and right to approve
 - × Protection for company information and intellectual property
 - × CRO responsibility for performance
 - × Company ability to directly intervene to insure performance or remedy errors
 - + Affiliates
 - × Notice and right to approve
 - × Bound by agreement as though party

THE MASTER SERVICES AGREEMENT, CON'T

- ✘ Who will do the work, con't
 - + Key employees
 - ✘ Keeping the team together
 - ✘ Performance issues
 - ✘ Defining and managing personnel changes
 - + Qualifications and training
 - ✘ CVs
 - ✘ Training responsibilities and associated costs
 - + Noncompete
 - ✘ Barrier to inadvertent transfer of confidential or proprietary information

THE MASTER SERVICES AGREEMENT, CON'T

- × What standards will the CRO be held to?
 - + Commercially reasonable efforts
 - + Professional standards
 - + Applicable law, including FDA guidances
 - × 21 CFR Part 312 (or 812 for devices) for GCP and ICH Consolidated Guidance E6
 - × Part 11 for electronic records
 - × HIPAA
 - × Ex US (EU Clinical Trial and Data Protection Directives)
- × Transfer of Regulatory Obligations (21 CFR 312.52)
 - + Transfer must be described in writing
 - + Any obligations not transferred in writing are retained by sponsor
 - + CRO that assumes has regulatory obligations of sponsor
 - + Responsibility for tasks is not necessarily an assumption of regulatory responsibility

The Master Services Agreement, con't

- ✓ **Obligations that may be assumed include:**
 - × **Safety reporting**
 - × (21 CFR 312.32; 21 CFR 812.150)
 - × **Selection of investigators and monitors**
 - × (21 CFR 312.53| 21 CFR 812.43)
 - × **Monitor the clinical trial**
 - × (21 CFR 312.56; 21 CFR 812.46)
 - × **Study drug/device management**
 - × (21 CFR 312.53, 312.57, 312.59; 21 CFR 812.43, 812.150, 812.46)

- × **How will the CRO be paid?**
 - + **Unit cost/fixed fee**
 - + **Time and materials**
 - × **Hourly rates and increases**

THE MASTER SERVICES AGREEMENT, CON'T

- ✘ How will the CRO be paid, con't
 - + Budget and line item detail
 - + Budget overruns
 - ✘ The EVA - monitoring fees to budget
 - ✘ Notice, justification, and solutions
 - + Invoice disputes
 - + Payment schedule
 - + Advances

THE MASTER SERVICES AGREEMENT, CON'T

- ✘ How will the CRO be paid, con't
 - + Pass through costs
 - + Invoice format and content
 - + Payment audits
- ✘ Who is responsible for the clinical site agreement?
 - + Company or CRO
 - + Who negotiates
 - + Who signs
 - + Who pays

THE MASTER SERVICES AGREEMENT, CON'T

- ✘ How will potential liabilities be allocated?
 - + Insurance
 - ✘ Limits
 - ✘ Additional insured
 - ✘ Waiver of subrogation
 - + Indemnification
 - ✘ Breach of agreement
 - ✘ Gross vs ordinary negligence
 - ✘ Material vs no qualifier
 - + Damages disclaimers
 - ✘ Consequential damages
 - ✘ Carve outs

THE MASTER SERVICES AGREEMENT, CON'T

- ✘ How will potential liabilities be allocated, con't
 - + Limitation of liabilities
 - ✘ Material breach
 - ✘ Gross negligence
 - + Outs
 - ✘ Delay by others
 - ✘ Dollar limits on damages
 - ✘ Special statute of limitations
 - + Transfer of Regulatory Obligations

THE MASTER SERVICES AGREEMENT, CON'T

- ✘ What about quality assurance?
 - + SOPs
 - ✘ Review and approval rights
 - ✘ Change control
 - + Company audit rights
 - + FDA audits and regulatory inquiries
 - ✘ Participation or presence
 - ✘ Allocation of costs
 - + Corrective actions
 - + Debarment

THE MASTER SERVICES AGREEMENT, CON'T

- ✘ What records and in what form?
 - + Electronic records and security issues
 - + Retention provisions
 - + Software issues
- ✘ What other issues should you think about?
 - + Term
 - + Termination
 - ✘ Transfer of responsibility to another CRO
 - ✘ Early termination fees
 - ✘ Right to records and clinical trial data

THE MASTER SERVICES AGREEMENT, CON'T

- ✘ What other issues should you think about, con't
 - + Confidentiality
 - + Intellectual property
 - ✘ New drug related IP vs. trial management improvements
 - + Dispute resolution

MANAGING THE RELATIONSHIP

✘ Some tips

- + In house team with clearly defined roles and responsibilities
- + Use bid defense, MSA development and kick-off meeting to set expectations
- + Avoid surprises; understand how fees and pass through costs are charged and what the company will need to spend
- + Meet all team members; don't hesitate to request alternative if you have doubts
- + Be frank about unit or fixed fees.
"Fixed" means fixed, no matter what
- + Tasks included in fixed or unit fees must be clearly defined

MANAGING THE RELATIONSHIP, CON'T

✘ More tips

- + Take project telecons seriously; use them to assure expectations are met and to help CRO adjust to trial developments
- + Problems are not like wine; they don't age well
- + Escalate if you are not satisfied with response
- + If a serious problem arises, take as much time as you need (and can) to determine a response and preferred pathway

THE MSA IN OPERATION, CON'T

- ✘ The Phase I trial is budgeted on a combination of a fixed fee and T&M basis. Project management is on a T&M basis. About half of the patients have been enrolled in the trial so far. You've just received an invoice from the NW for the last 4 months of activities. It appears that ElvinsRx has been billed for about 85% of the budgeted project management costs already. In addition, you learn from the invoice that the NW handled a protocol amendment. Based upon the cost of the amendment, you assume it was a major change. Upon talking internally, you learn that wasn't the case and NW charged 50% more than agreed.
- ✘ As you prepare to talk with the CRO about these issues, what provisions of the MSA may be helpful?

THE MSA IN OPERATION, CON'T

- ✘ Work Order budget
- ✘ Terms for fixed fee vs. T&M
- ✘ Budget overruns
 - + EVA
 - + Notice; justification; solutions
- ✘ Change orders
- ✘ Invoice requirements
- ✘ Invoice disputes
- ✘ Payment audits

THE MSA IN OPERATION

- ✘ After a pleasant weekend, you arrive in the office Monday morning only to learn that one patient in the Phase I trial has suffered a heart attack and is hospitalized in serious condition. Heart problems were identified as a potential risk of the study drug in preclinical studies and the protocol requires periodic heart function tests. The FDA, IRB, and other investigators are notified appropriately. A few weeks later you learn that the investigator does not have a signed ICF for this patient in his file and failed to document the required heart function tests. The investigator claims the ICF was signed and the heart function tests performed. You also learn from the project manager that the CRA who was performing the ongoing site monitoring is an independent contractor to NW and is not, in fact, the person the NW originally told you would be doing the monitoring. In addition, as NW knew at the outset, ElvinsRx is in negotiations with BigPharmaRx for a collaboration around E-103. This SAE has caused BigPharmaRx to pull out of the negotiations.

THE MSA IN OPERATION, CON'T

- ✘ What terms of the MSA may be important here?
 - + Transfer of regulatory obligations
 - ✘ Regulatory responsibility for monitoring; investigator selection
 - + Applicable law provision
 - ✘ Adherence to FDA guidances as well as regulations
 - + Key employee provision
 - ✘ Notice of change of team member
 - ✘ Approval of replacement
 - + Qualifications and training
 - + Independent contractors
 - ✘ CRO legal responsibility for conduct

THE MSA IN OPERATION, CON'T

- × What terms of the MSA may be important here, con't
 - + Indemnification
 - × Breach of agreement vs. material breach
 - × Violation of applicable law
 - × Gross vs. ordinary negligence
 - + Insurance
 - × Additional insured
 - + Damages
 - × Disclaimer of consequential damages
 - + Liability limitation
 - × Limiting liability to material bad conduct
 - + Limitation on the dollar amounts recoverable

LESSONS LEARNED

- ✘ Careful planning
- ✘ Careful preparation
- ✘ Careful attention
- ✘ Build relationships
- ✘ Address problems early
- ✘ Get the specifics

PRESENTER

- ✘ Deborah A. Elvins is a managing member of Adkins, Plant, Elvins & Black, PLLC (www.adkinsandplant.com) and focuses her practice on advice to and transactional work for biotechnology and pharmaceutical companies, including the negotiation and drafting of CRO and clinical trial agreements, and licensing, manufacturing, supply, research and other agreements. Before joining APEB, Deborah was Vice President, Legal Affairs for Dendreon Corporation and before Dendreon a partner in Stoel Rives LLP, a large Pacific Northwest corporate law firm.