Risks vs Benefits of Various CRO/ Sponsor Managed Clinical Trial Models

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Yikes

Preanalytical nightmare, part 2
Label inside the urine tube

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Why CRO Outsourced Models: Perfect Arrangement on Paper

- CROs reduce **Cost** of Trial with
  - quick access to a repository of ready patients
  - aggressively manage their staff and overhead costs—a practice that translates into more efficient utilization and trial conduct.
  - for fixed assets like a CRO's Phase I unit, more volume can be pumped through the same unit than is possible with a single sponsor,
- CROs reduce **Delay** with faster testing of inclusion/exclusion criteria and allows sponsors to prescreen the subjects and refer them

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Lifetime Commitment

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Why CRO Outsourced Models: Perfect Arrangement on Paper

- CROs increase **efficiency** and **flexibility**.
  - Sponsors can reduce their need for fulltime internal staff and become more flexible in expanding their access to a wider range of expert external resources.
  - In the same respect, CRO CRAs are utilized more efficiently because they can support multiple sponsors' trials in the same region, reducing the need for travel and increasing overall CRA utilization.

The sponsor wins by reducing their overhead and being able use exactly the right resources at exactly (and only) the right time. The CRO wins by profiting on their engagements. On paper, it's the perfect arrangement.

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Inadequate Trial Design: Missing AE/SAE

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Apparently Not: Pitfalls when CRO Manages Third Party Vendors (TPV)

- The disconnect between business model and management approach often has disastrous results.
- Even if there are no major incidents in the course of the trial, seemingly smoothly running studies can have hidden data quality issues found only after submission.
- Duplication of work and more cost; bad vibes between actors when sponsor is engaged in some cases
- TPV also prefer to deal directly with sponsors in many cases, believing they can understand the sponsor's expectations better

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Apparently Not: Pitfalls when CRO Manages Third Party Vendors (TPV) (Cont)

- Lack of direct vendor management can lead to negative implications to quality, cost, and speed.
  - It's perceived that CROs are less committed than sponsors to oversight,
  - issues tend to be minimized or escalation delayed while the CRO works to fix them.
  - Sponsor team keeps oversight on the CRO as well as the TPV which is duplicitous work; increases cost.
  - Many TPVs do not want to share proprietary pricing with CROs that might offer the same services.

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Sponsor Vs CRO Control of TPV

% RESPONDED	SELECTS	NEGOTIATES	MANAGES
34%	Sponsor	Sponsor	Sponsor
26%	CRO	CRO	CRO
23%	Sponsor	Sponsor	CRO
10%	Sponsor	CRO	CRO
6%	CRO	Sponsor	CRO

Source: R.H. Bouchard and Associates

Table 1. With regards to the selection, negotiation with, and management of third-party vendors, which of the following is generally true in your organization?

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Reasons for Not Going To Trials w/CRO Managing and Overseeing TPV

REASON	PERCENT OF RESPONDENTS
We have been successful managing third-party vendors by ourselves.	46%
I don't feel that the CROs are looking out for my best interests when negotiating with third-party vendors—it's only a pass through.	42%
CROs don't negotiate aggressively enough with third-party vendors.	42%
CROs don't do a good job managing third-party vendors.	24%
I don't want the CRO distracted by having to manage third parties.	28%
I have enough staff to effectively manage third-party vendors.	14%

Source: R.H. Bouchard and Associates

Table 2. Why do you *not* have CROs manage third-party vendors? (Select all that are applicable.)

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Monitoring The Monitor in Their Avatars

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CQA and Outsourcing Dilemma When CRO is the Manager for TPV

- Lack of consensus of key Study Quality Metrics (SQM) to monitor or Key Quality Indicators (KQI) to track. It varies by:
  - KOL or Therapeutics or Size of sponsor or Phase of study
- Gold standard Quality Agreements between sponsor and CRO not being adhered to or ignored for small or mid-size pharma
- Sponsors partnering with a CRO for analytic services often lack the ability to directly access and retrieve their raw data
- Sponsor-CRO-ARO-TPV Consortium: Each have their own fiefdom and sponsor cannot achieve agreements.

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CQA and Outsourcing Dilemma When CRO is the Manager for TPV (cont)

- Delays in receiving both ad hoc/custom and periodic standard reports (incl TPV contribution) from their CRO can potentially result in critical inefficiencies and data inaccuracies for clinical operations managers, as well as for CRAs

- The sponsor must also allocate its own resources (Auditors and /or SMEs) to oversee both the CRO and the TPV, leading to possible duplication of work, bureaucracy and delays

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ICH GCP(R2) Status & Impact

- Now in Step 5, Implementation Period
  - EMA has adopted (R2) for implementation on 14 Jun 2017
  - Swissmedic adopted with immediate effect, will change law later
  - China FDA has incorporated (R2) into draft of new GCP law
  - Expect FDA to adopt more quickly than original (i.e. <1 year)
  - Not aware of any information from PMDA
- Sponsors will need to be ready for ICH GCP(R2) from Mid- 2017 onwards
- Regulatory Inspectors will start to use (R2) as a reference for their inspections

So how does this impact the Outsourcing Process to CROs managing trials as well as TPVs?

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Transfer of Responsibilities To CRO
What Are Sponsor's Options

A new addition to expectations:

SPONSOR: Contract Research Organisation 5.2.2
Any trial related duty or function that is transferred to and assumed by a CRO should be specified in writing. The sponsor should ensure oversight of any trial-related duties or functions carried out on its behalf, including trial related duties and functions that are sub-contracted to another party by the sponsor's contracted CRO(s)

- More 3rd party vendor due diligence and audits/assessments
- Quality Agreements should be more robust to encompass oversight of TPVs
- From the very beginning of the award, sponsors and CROs need to put painstakingly clear agreements and processes in place to define how monitoring will be measured and by whom.

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Transfer of Responsibilities To CRO What Are Sponsor's Options (Cont)

- That process/system must include a way of quickly identifying significant deviations in outsourcing services and ways to trigger effective and timely CAPAs (corrective and preventive actions).

- CAPAs must lead to the identification of the root cause(s) of a significant GxP deviation.

- Governance Model should have
  - A contract that clearly defines deliverables and roles and responsibilities of each partner
  - Ways of measuring compliance
  - A quality plan that proactively anticipates quality and compliance risks and describes and monitors effectiveness of these plans.
- Some sponsor companies and CROs have implemented penalties when targets (e.g. missed timelines or poor compliance) are not met.

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Items to Consider – Sponsor vs CRO TPV Contracts: Pros and Cons

Sponsor Holds Contract	CRO Holds Contract
Responsible for Due Diligence and Audit	Ideally, CRO does the due diligence and provides certificates to sponsor
In case of issues and concerns no middleman CRO to complicate situation	CRO can potentially complicate relationships if issues found during sponsor due diligence
Sponsor may not enjoy volume discount	If TPV is a vanguard vendor for CRO working on a few trials with the CRO, discount can be significant; CRO needs to channel these disc to sponsors; always an issue
Sponsor may need contract auditors for Regional TPV in global trials	CROs with large global footprints may have regional and language advantage with these regional TPVs
Sponsor QMS should be sufficient	Governance and Oversight Processes with RBM, SCMS and KQIs built in
Sponsor directly acts with TPV for RCAs, Issue escalation and implementation of CAPA	Sponsor is at the mercy of CRO/ARO for issue escalation, RCA and completion of CAPA

Does this sound familiar?

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Ultimately

The sponsor can always Delegate the Tasks but not the Responsibility.

Sponsor can delegate (e.g. outsource) tasks to third parties but will always remain fully responsible and accountable for all decisions, actions undertaken, and data generated by its partners. It's the sponsor's oversight or control of its partners that is paramount to achieving successful quality management.

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Last but Not the Least

Questions and Answers

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