

Delays & Administrative Burdens when Initiating Large Clinical Trials: Regulatory Processes, Contracts & Insurance

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Trial Costs Have Increased Substantially

- ISIS-1 (mid-1980's): 16,000 AMI pts
 - £1,000,000
 - A similar study today costs about \$55 mill to 75 mill USD
- HOPE (mid-1990's): 9,500 CV prevention
 - \$ 15,000,000 USD
 - A similar trial today will cost about \$80 to 120 mill USD.

Why have costs increased so greatly?

What impact will this have on both trials of generic questions and of new chemical entities?

Then ...

HOPE: Average time to start 80% sites in any country: 4 months

- **Relatively short time for regulatory/ethics review, in general 1 to 3 months (although this was the biggest delay)**
- **No contracts (letter of agreement)**
- **Minimal regulatory documentation required**

...and Now

HOPE-3: Average time to start 80% of sites: 10 months.

- Regulatory approvals: Done by National Leaders, 6-14 months
- Drug import approvals: 1-2 months
- Ethics done concurrently (where possible)
- Contract negotiation: 3-4 months

24 months after starting, 14/22 countries have started: 50% of sites

National Leaders reticent to do this process again

Result is fewer investigator run studies

Administrative Delays

Each step in the start-up process takes about twice as long and costs twice as much compared to 10 to 15 yrs back:

- Regulatory approvals
- Ethics approvals + other regulatory documentation
- Drug packaging & distribution
- **Contracts and Insurance**

Regulatory Approvals

- Lengthy process in certain countries (can take up to a year in many countries)
- Investigator run versus industry run studies face greater hurdles:
 - Much longer to get approval in many countries because of additional steps:
 - e.g. Health Ministry plus DCGI approvals in India are required, can take 9-18 mos. Industry studies approved in 2 mos
 - Regulatory requirements are onerous for academics who have neither the experience or the resources, and costly (time and effort wise)
 - In some countries no mechanism for an investigator to make the application

What is meant by contracts, indemnification & insurance?

- **Contracts:**
 - **Main agreement:** Between the coordinating centre and the sponsor
 - **Site agreement:** Explains the mutual expectations between the sponsor, the institution and the investigator
 - **Usually includes:**
 - **Indemnification:** The provision that one party will pay the costs for losses incurred by a second party
 - **Insurance:** Liability insurance for institution & investigator

National Cancer Institute Experience

- 180-300 days to negotiate the main contract between a sponsor and an academic group (Martin Murphy, COO, NCI)
- 79 days for contracts at sites (VICC)
- They claim that delays cost companies \$1 M USD/day!
- What about academic, non-industry trials?

PHRI Experience

- 5- 10 FTE required to negotiate contracts for one large study:
 - Can take 6-12 months
 - Requires lawyers, notaries, administrative help, study team, translations
- Total cost can range from \$500,000 to \$1,000,000 USD depending on complexity (not affordable in non-industry trials)
- Usually resources available in industry studies , but not for peer review studies
- Cost of delay to trial – difficult to quantify

Negotiating Site Agreements



The Process Differs...

- Depending on the amount of administrative structure at the site
- More admin structure at a site means it usually requires MORE steps and time to negotiate
- Investigator run studies treated the same as industry studies, and these requirements are often difficult to meet for non-commercial organizations
- Those without formal administrative structure tend to generally accept contract without too much debate or delays.....but their contracts and “rights” are about the same!

What are the most contentious issues?

- You would think:
 - Publication rights
 - Budget
- More commonly:
 - Indemnification – for ethics boards, etc.
 - Investigator insurance
 - Intellectual property
 - Translations

Indemnification

- *Usually* for all study related activities
- Clinical sites now request more extensive indem to include ethics boards, hospitals
- Difficult if not impossible to obtain for non-pharma sponsored studies:
 - Usually separated into protocol and drug (intervention), add'l documents to sign

Is indemnification always required?

- Study of two common procedures/treatments:
 - Off pump CABG vs on pump?
 - Radial vs femoral access for angiography?
 - Transfusing one week old or fresh blood?
 - 2 doses of ASA (100 vs 300 mg)

Procedures/interventions commonly done or used, yet institutions are demanding indemnification: Results in important clinical and public health questions being left unaddressed.

Hospital/Investigator Insurance

- Usual to include a stipulation regarding the amount of malpractice insurance to be held by the investigator or the hospital.
- Insurance amounts held by investigators can vary greatly; or in some countries (eg Africa or India) investigators and institutions may not hold any insurance at all
- Insurance can be purchased (by investigator, or “sponsor” or academic lead center) but can be expensive in some countries
- **END RESULT:** Dissuades investigators from participating in clinical trials and makes it difficult to conduct trials in these countries.
- **NOTE:** In the past , nobody bothered about this and good trials were conducted!

Intellectual Property (IP)

- Main contract stipulates sponsor owns rights to any developments related to the drug
- Institutions are now requesting rights to IP from their data; tricky when IP may be based on the entire study data

Contract Translations

- Greatly increases time and cost
- Some institutions will not look at contracts in other language
- Even minor changes need notarized translations
- Negotiations lengthy and sometimes difficult

And what does all this mean for the trial

- Issues require back and forth discussion:
 - Initial site review: 3-4 weeks
 - Response: 2-4 week
 - Site Response: 2-4 weeks...etc.
 - Total process ranging from 3 to-4 months per sites. Imagine this process in a study of 100, 500 or 1000 sites! Imagine trying to do this process in academic studies with modest resources!
- Delayed site start-up = less time to recruit = need for more sites....
- Some centres may never be able to negotiate a final contract

Increasingly difficult to do low cost studies: Non-industry trials of generic questions are an endangered species!

Efforts to Standardize Clinical Trial Agreements

- Duke Clinical Research Institute (2003): Clinical Trial Site Agreement (<http://www.dcri.duke.edu/ccge/contracts/>)
- Association of American Medical Colleges (2004): Clinical Trial Contracts: A Discussion of Four Selected Provisions (<http://www.aamc.org/publications>)
- Council of Academic Hospitals of Ontario (2007) (http://www.caho-hospitals.com/Harmonization_of_Clinical_Study_Agreements_Initiativea.aspx)
- NCI/CEO Roundtable on Cancer(2008): Proposed Standardized/Harmonized Clauses for Clinical Trial Agreements (<http://cancercenters.cancer.gov/documents/StClauses.pdf>)
- Institute of Medicine Clinical Trial Agreement (2009) (<http://www.iom.edu/CMS/3740/24155/65667/65960.aspx>)

Why has this not moved forward?

- Many, many players
- Most players do NOT have an interest in simplification of the process by elimination of redundant or bureaucratic steps.
- “Groups” have started the process - need national leadership, consensus and endorsement to bring closure
- Need discussions beyond North America

How Do We Address These Contract Issues?

- Nationally accepted clinical site contracts for:
 - Industry sponsored trials
 - Investigator run initiatives
 - Non-intervention studies e.g. registries
(Hopefully without further modifications)
- Centralized/nationally available insurance and indemnification, where required for investigator/hospital/university in low risk trials
- For simple, low risk studies (concept of proportionality) eliminate:
 - Contracts
 - Indemnification and insurance

How can we collectively take on this task?

Should bureaucracies be penalized for delays?