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# Contract Negotiation with Hospital & Principal Investigator

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# Overview

- Review of Literature
- Background & rationale
- Worrisome factor : Industry Perspective
- Key Perspective: Industry-Investigator relationship
- Clinical Trial Agreement : The need!
- Negotiations: Getting into the details.
- Challenges in negotiations
- Win-win relationship?

# Review of Literature

- Stelfox et al.(1998) authors supported safety calcium channel antagonists had high frequency of financial relationship
- Davidson (1986) reported that results favoring a new therapy over traditional if it is funded by new therapy manufacturer
- Cho & Bero (1996) reported that Industry funded projects showed more efficacy of drugs versus non funded.
- Friedberg et al.(1999) unrealistic pharmaco-economic outcomes in funded projects by Industry
- Controversies concerning disclosure of unfavourable findings in studies of antidepressants in children (Meir, 2004)and rofecoxib (Topol, 2004).

*Can Practicing Physicians trust the information they are receiving?*



# Background & Rationale

- Competitive nature: Budget planning, negotiations stressful, time consuming and full of pit falls<sup>1,2,3</sup>
- Balance: Performance of clinical trials, congruent with investigators fiscal interests (obligation of contract)<sup>4</sup>
- Understanding : Lack of thorough understanding of the direct and indirect costs<sup>5</sup>
- Conflict: Language of Clinical Trial Agreement; potential provisions that restrict investigators control over trials (Schulman, 2002; Cohen, 1994).

1. Miller RD (2002). Best Pract Res Clin Anaes. 16:353-70; 2. Cavan BN (1995). Biotechnology. 13: 226-8.  
3. Blackhouse (1998). Heath Econ. 7: 605-19 4. Claxton & Posnett J (1996). Health Econ. 5: 513-24  
5. Kristy et al. (2004). Anaesth Analg. 99: 173-9;

***Retrospective review and prospective planning is the key!***

# Worrisome factor?

- Slow review of the Industry sponsored proposals
- IRB/IEC review based on the timelines than load!
- Delay in starting date of trials (cost daily about 1.3 Mio\$)
- Multiple responsibilities like teaching, research, patient care may delay trials
- 80% of the Industry sponsored trials to Academic centres, reduction to tune of 40%.
- Commercial sectors completes trials more rapidly and more cheaply than academic centres.

***Academic health centre overpromise and underdeliver!***



# Industry-Investigator Relationship

## 0 Trial Design:

Investigators to in-house control; surrogate endpoints vs clinical endpoints

*Bero & Rennie (1996), Rochon et al (1994)* commented that "companies catalogue to produce desired results". NSAID study (65 years and above < 2.1% )

*Johansen & Gotzsche* commented on studies on Ampho B Vs Fluconazole

## 0 Data Analysis:

Raw data stored centrally, investigators receive portion of the data

## 0 Publication:

Publication vs FDA approval; Publication becomes important post approval

Name Vs Design Vs Recruiting more patients

Timelines to publish post concluding the study (3 to 6 months to no publications)

*Olivieri (1998)* Deferiprone Apotex case (forbid disclosure for 3 years); *Dong (1990)* I-thyroxine in parathyroid (No disclosure without manufacturer's permission)

Industry obstruction to publishing is a big problem (*Thomas Bodenheimer, 2007*);

AIDS Vaccine, Immune response

## 0 Authorship:

Non author writing syndrome: Drug trial reports, editorials and review articles

Professional medical writer (Ghost writers) and clinical investigator (Guest Editor); Guest-Ghost Syndrome

Criteria laid out by International Committee of Medical Journal Editors (ICMJE)

***Underreporting research is scientific misconduct!***



# Clinical Trial Agreement

A legally binding agreement that manages the relationship between the Sponsor [typically Industry/CRO] who may be providing:

- Study Drug or Device or Diagnostics
- Financial Support
- Proprietary Information

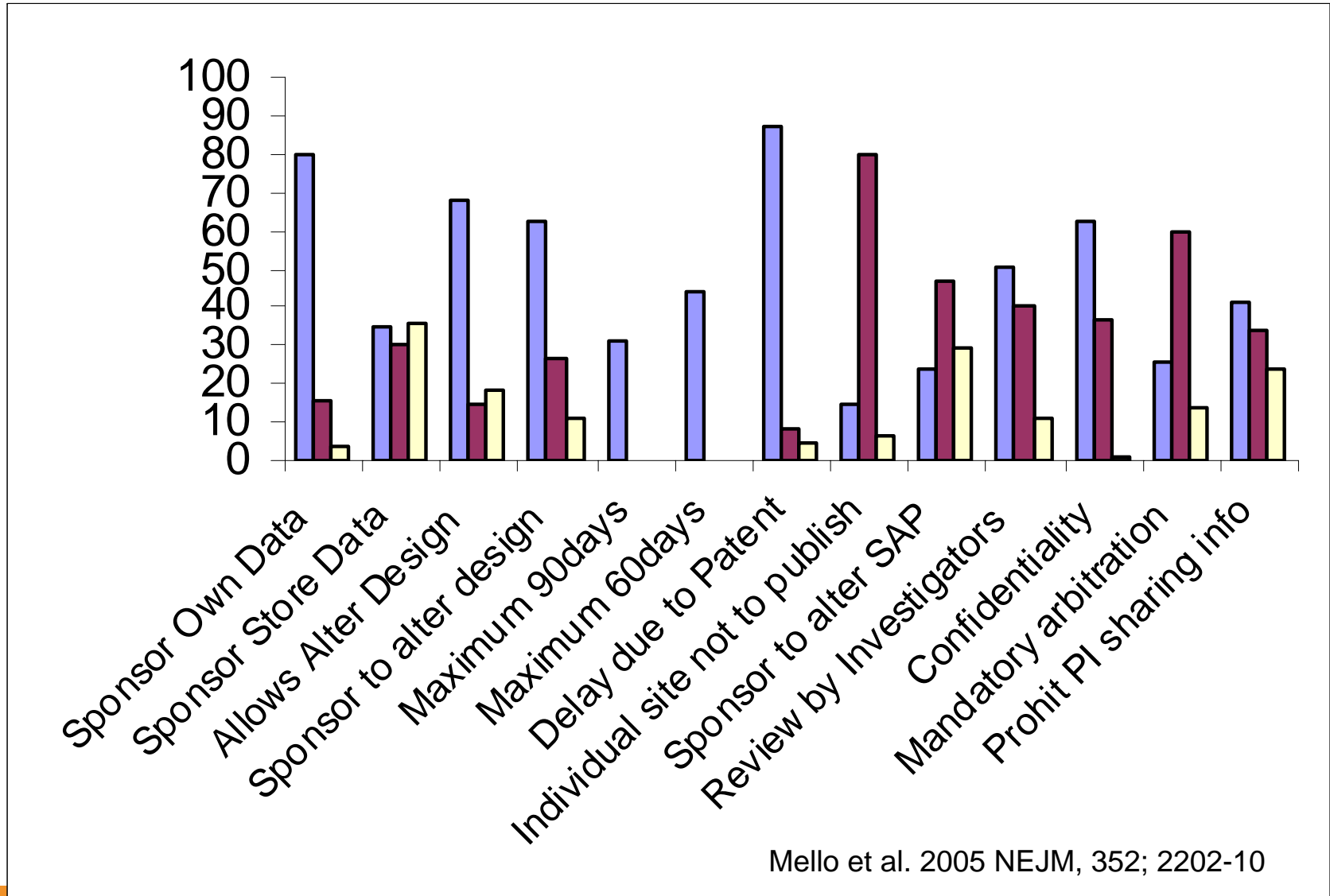
And the Institution who may be providing:

- Data and/or Results
- Publication, Input into Publication
- Input into further Intellectual Property

*Governs and delineates the terms and obligations!*



# Case Study



Mello et al. 2005 NEJM, 352; 2202-10

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***Provisions for Data, Publication is the key in long run!***



# Perceived Difficulty

**Table 3. Perceived Difficulty of Negotiating Provisions of Multicenter Trial Agreements with Industry Sponsors.\***

Provision Negotiated	Response			
	Very Difficult	Somewhat Difficult	Not Difficult	Not Usually Negotiated
		<i>percent</i>		
Ownership of inventions and intellectual property	31	35	31	4
Ownership of the data produced by the research	25	38	32	5
Indemnification issues	17	51	31	2
Confidentiality of the data produced by the research	15	41	42	2
Rights to publish	15	54	30	1
Rights to disseminate study results	15	61	24	1
Confidentiality of trial participants' records and information	7	18	65	11

\* Data are from 107 administrators. Percentages of completed responses are shown. Because of rounding, percentages may not total 100.

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*Ownership of IP & Data drives negative negotiations*



# Negotiations Structure

**Table 4. Prevalence of Disputes with Industry Sponsors of Clinical Trials.\***

Subject of Dispute	No. (%)
Payment	62 (55)
Early termination	11 (10)
Timing of payment	9 (8)
Eligible expenses	7 (6)
Nonperformance by institution	4 (4)
Final payment	4 (4)
Appropriateness of budget amount	4 (4)
Other	5 (4)
Unspecified	18 (16)
Intellectual property	11 (10)
Data control	9 (8)
Indemnification	7 (6)
Publication	6 (5)
Personnel	5 (4)
Confidentiality	4 (4)
Misconduct	2 (2)
Enrollment of subjects	1 (1)
Control of study	1 (1)
Problem with IRB	1 (1)
Other	4 (4)

**Table 5. Policies, Tools, and Structures Used to Facilitate Negotiations Concerning Clinical-Trial Agreements.\***

Variable	Overall (N=107)	High-Volume	Low-Volume
		Institutions (N=55)	Institutions (N=51)
		<i>percent</i>	
<b>Negotiation tools</b>			
Written general statement of ethical or legal principles to which the institution adheres	65	74	57
Written checklist of topics that clinical-trial agreements should cover	77	89†	67
Written list of specific provisions that agreements should contain	75	82	69
Written list of specific provisions that are unacceptable	67	76‡	57
Written boilerplate agreement to use as a starting point in negotiations	84	100†	68
<b>Negotiation practices</b>			
Often or sometimes consult with counterparts in the offices of sponsored research at other schools or hospitals about policies and standards	78	87‡	67
All, most, or some frontline negotiators handling clinical-trial agreements have law degrees	41	54‡	29
Draft clinical-trial agreements always or usually signed or reviewed by a lawyer	34	34	35
Draft clinical-trial agreements always or usually signed or reviewed by a senior research administrator	79	70‡	88
Draft clinical-trial agreements always or usually signed or reviewed by the faculty principal investigator	91	89	92

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*Substantial differentiation exists between institutions!*



# Getting into Details

- Number of patients from the site : 5 Vs 100.
- Payment schedule: Regular intervals or upon completion of specific measurable milestones (time & effort).
- Start-up costs: 1-3 patients full price upfront; termination before FPFV
- Delay in start up of the study (> 3 months); screen failures
- Contingency for Audit preparation
- Inflation adjustment (> 1 year)

*Negotiations effort in this direction may significantly impact positively*



# Typical Clinical Trial Agreement

- |  |  |
|--|--|
| <ul style="list-style-type: none"><li>• Preamble</li><li>• Acknowledgements &amp; Responsibilities</li><li>• Term &amp; Termination</li><li>• Payment/Reimbursement of Costs</li><li>• HIPAA, Patient Privacy</li><li><input checked="" type="checkbox"/> Publication</li><li><input checked="" type="checkbox"/> Intellectual Property</li><li><input checked="" type="checkbox"/> Confidentiality/<br/>Proprietary Information</li></ul> | <ul style="list-style-type: none"><li><input checked="" type="checkbox"/> Indemnification</li><li><input checked="" type="checkbox"/> Insurance</li><li><input checked="" type="checkbox"/> Subject Injury</li><li><input checked="" type="checkbox"/> Waiver of Consequential Damages</li><li>• Miscellaneous<ul style="list-style-type: none"><li>– Export Controls</li><li>– Governing Law</li><li>– Dispute Resolution/<br/>Arbitration/Mediation</li></ul></li><li>• Exhibits</li></ul> |
|--|--|

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*Best fit model!*

# Negotiation



- Sponsor supplies a template.
- Specialist redlines the document.
- Go back and forth with sponsor until all points are covered.
- Get to "Yes".

*Share a common goal from which we draw different rewards!*

# Challenges in Negotiating

- Top 4 Hurdles
  - Compliance with Institutional policy
  - Indemnification
    - If company will not indemnify
    - If company requires mutual indemnification
  - Insurance
    - If company does not carry minimum levels of insurance
    - If company cannot prove liquid assets to cover liabilities
  - Publication
    - If company requires “approval” of publication
    - If company a requires a *de facto* publication restriction



*Clear understanding of the goals*

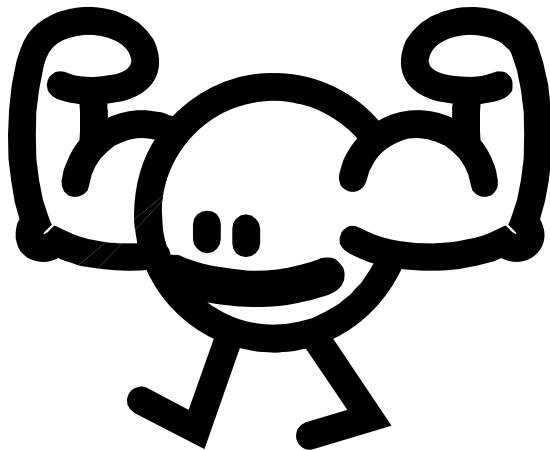
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# How to “Pump Up” our Negotiating Standpoint.



- United Front.
- Clear layout of Goals.
- Know who we are dealing with.
- Understand the Challenges.

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*Perceive each one has a role to play!*