Transparency or more surprises in the small print

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Pharmaceutical Contract Management Group

JONES DAY | One Firm Worldwide℠

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Transparency or surprises in the small prints

A presentation to PCMG

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A Complicated Constellation

- Multiple actors and roles in a clinical environment: site, sponsor, PI, CRO, and other third parties (e.g., monitors, logistics companies, laboratories, etc.)
- Respective regulatory/product liability/contract positions
- The position of insurance companies
- ***Transparency = Partnership***

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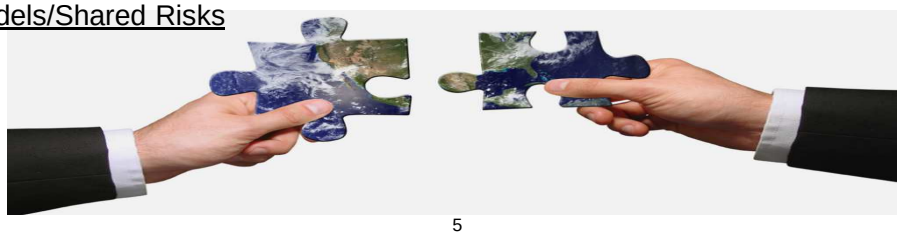
Emerging Collaboration Models between Life Sciences companies and CROs

- Extensive (and growing) Outsourcing of Clinical Trial Functions
- Engagement of Global CROs
- Emergence of Academic CROs
- Increasing Partnership Models/Shared Risks
- Broad Master Service Agreements
  - Multiple compounds
  - Multiple trials
  - Performance Metrics



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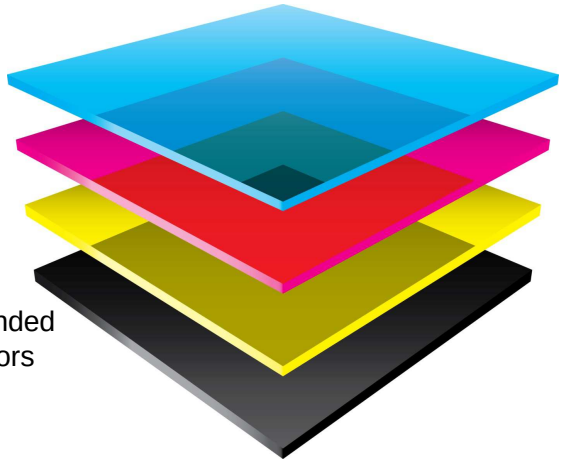
Sponsor/CRO: Several Layers of Potential Liability

- Regulatory:
  - Sponsors' overall liability for Clinical Trial Conduct
  - CRO is sponsor's delegate
  - **No transfer** of responsibilities
  - Co/shared responsibility/exposure?
- Product liability
  - Typically with sponsor but can be extended to contract manufacturer and other actors
  - Professional Malpractice
- Criminal liability



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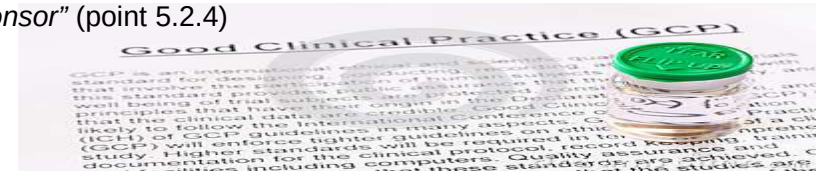
CRO - GCP

- A Sponsor may "transfer" some of all trial-related duties to a CRO. However, ultimate responsibility for quality and integrity of trial data always resides with sponsor
- CRO must implement quality assurance and quality control
- Delegation must be documented in writing
  - "*All references to a sponsor in this guideline shall also apply to a CRO to the extent that a CRO has assumed the trial related duties and functions of a sponsor*" (point 5.2.4)



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Potential Litigation Environments

- Sponsor vs patients
  - product liability
  - sponsor responsibilities
- Sponsor vs service providers (e.g., CROs)

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Last Resort

- Why it should be avoided:
  - Image price
  - Potential repercussions on the trial as a whole in terms of e.g. reliability of results or continuity of services

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The New York Times

EUROPE

6 Hospitalized, One of Them Brain-Dead, After Drug Trial in France

By SEWELL CHAN JAN. 15, 2016

Drame de Rennes : le protocole de l'essai clinique en accusation

Mots clés : Essai clinique

Par Anne Jouan - le 21/01/2016

EXCLUSIF – Le Figaro s'est procuré le protocole du laboratoire Bial, promoteur de l'essai de Rennes qui a provoqué la mort d'un volontaire.

Depuis l'annonce de **l'accident mortel survenu lors d'un essai clinique à Rennes**, les agences européennes comme les industriels réclament, au nom de la transparence et de la sécurité sanitaire, que la France communique le protocole du laboratoire portugais Bial. Mais l'agence française du médicament (ANSM), qui a validé le protocole de l'essai, s'y refuse, arguant, de manière assez ridicule, le «secret de l'instruction» alors même qu'elle n'y est pas tenue. Elle peut rendre publiques les pièces qu'elle désire. L'essai mené à Rennes par l'entreprise française Biotrial **pour le compte de Bial** s'est soldé par la mort d'un volontaire sain, dimanche, et par l'hospitalisation de cinq autres, dont quatre sont susceptibles de garder des séquelles neurologiques.

Le Figaro s'est procuré ce protocole et l'a soumis à trois experts renommés. Le document de 96 pages rédigé par Bial est en anglais. Il en ressort plusieurs interrogations quant au sérieux de l'essai. «L'ANSM leur a lâché la bride», estime un de nos chercheurs. «C'est un protocole assez compliqué qui

LOIC VENANCE/AFP

L'essai mené à Rennes par l'
s'est soldé par la mort d'un v
cinq autres.

January 19, 2016 5:19 pm

A tragedy at Rennes and the problem of drug trials

John Kay

Share Author alerts Print Clip Comments

The sector has to understand it has responsibilities to a wider community than its own shareholders

The Pontchaillou medical centre in Rennes, France, where a man died during a painkiller trial

CORRIERE DELLA SERA / SALUTE

FRANCIA

Test su nuovo farmaco antidolorifico
Un morto, cinque pazienti gravi

EL PAÍS

INTERNACIONAL

EUROPA EE UU MÉXICO AMÉRICA LATINA ORIENTE PRÓXIMO ASIA ÁFRICA

Muere uno de los ingresados en Francia a causa de un ensayo clínico

- Otras cuatro personas sufren problemas neuronales graves

ANA TERUEL | París | 17 ENE 2016 - 21:48 CET

Klimagipfel in Paris

Frankfurter Allgemeine Wissen

Donnerstag, 28. Januar 2016

POLITIK WIRTSCHAFT FINANZEN FEUILLETON SPORT GESELLSCHAFT STIL TECHNIK & MOTOR

Home > Wissen > Koma nach Medikamententest in Rennes

Hirntod nach Medikamententest

Gründe für starke Nebenwirkungen noch unbekannt

Sechs gesunde Freiwillige, die sich in Frankreich für einen Arzneimitteltest zur Verfügung gestellt haben, sind schwer erkrankt. Eine Testperson liegt hirntot auf der Intensivstation. Die Gründe sind noch unbekannt.

15.01.2016

How to Avoid It

- Key contract clauses/issues
  - jurisdiction/out of court settlement
  - audit rights
- Out of court settlement
  - advantages/disadvantages (cost and efficiency vs time)
  - chances of acceptance

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Key Contractual Issues

- MSA/Scope of Work: tasks definition (eg CRO MSA) - beware of over-simplistic MSA “check the box” annexes
- Some functions require professional qualifications/judgment (e.g., medical judgment): is CRO prepared/equipped to assume that burden?
- Assumption of Key Regulatory Obligations - an increasing trend. Examples:
  - CRO to assess sponsor’s legal and regulatory compliance infrastructure
  - CRO to notify client of legal/regulatory changes affecting their operations
  - CRO to lead interactions with key stakeholders: eg as regards PV and associated reporting obligations

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Key Contractual Issues

- Performance of key regulatory functions. Examples:
  - Subject recruitment
  - Monitoring
- Parties to CTA/Negotiation of CTA
- Personnel Training
- Use of Affiliates: check liability of each actor in the chain

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Key Contractual Considerations

- Monitoring/Auditing
- Compliant Practices with Health Care Professionals/Patient Organizations
- Indemnity/Insurance:
  - Sponsor liability often strict liability
  - Insurance requirements precisely defined by the local law
  - Insurance contracts often allow insurer to take control of litigation: potential conflicting goals between insured and insurer
- Termination/Transition

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Case Study 1

- March 2006: six healthy volunteers receive drug
- First in human trial – 6 subjects were administered the study drug almost contemporaneously
- All six subjects suffered severe reactions (multiple organ failures) within hours and were treated in intensive care
- CRO and Sponsor highlighted that they had complied with regulatory requirements and conducted the trial according to protocol which had been approved
- Press reports mentioned that the trial recruitment procedures emphasized monetary compensation and downplayed risks
- Regulatory authority initiated an investigation on the trial procedures
  and ethics
- Independent expert group appointed to investigate the case

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Which entities involved?

- Sponsor (GCP inspected)
- CRO (GCP inspected)
- Hospital (GCP inspected)
- Confidential party (GLP inspected)

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How did it end? No Litigation but…

- Sponsor “wiped out”
- CRO was the natural target left
- In its SEC filings covering the period up to the end of 2007, CRO reported having spent 1.8 million USD in legal fees and other costs. They also reported that their insurance was potentially insufficient to cover their exposure
- Press sources indicated that CRO ended up settling for millions of GBPs out of court

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Case Study 2

- SAE and alleged GCP violation involving Study team
- US sponsor/European patient
- Issues to consider:
  - Level of potential claims: striking differences
  - Venue(s) for Dispute: what is the likelihood to bring the case to the US?
  - Need 2 lawyers teams: beware of different rules on privilege
  - Notifications to regulators:
    - when necessary and when sufficient for sponsor to investigate and take appropriate action (audit)

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Dynamics between Sponsor/Site/PI/Patient/Insurers/Monitors/Auditors/CRO

- Sponsor Insurer/Sponsor
  - Focus on level of claim and likelihood of success (Insurer)/Focus on reputation effects (Sponsor)
  - Right to take control of litigation but absence of sector-specific knowledge (Insurer)/Full understanding of dynamics at site and applicable legislation (Sponsor)
- Counsel cooperation: keySponsor/Site
  - Contractual audit rights of sponsor
- Sponsor/Monitors-Auditors/CROs: independence is key
- Sponsor insurer/patient insurer (Government insurance body)
- Data Protection Concerns

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Transparency = Partnership Key Messages

- Nobody wins litigating in this area (with exceptions)
- Transparency/Partnership is key
- Be clear on capabilities and expectations, and draft well
- Know the law but no "boxed" approach: no hiding behind legalistic constructions
- Choose well who you are dealing with

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Thank you!

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