Negotiating Clinical Trial Agreements: Balancing the Interests of Sponsors and Healthcare Providers
Crafting Indemnification, IP Rights, Confidentiality and Other Key Provisions

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Today’s faculty features:

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CLINICAL TRIAL AGREEMENTS

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Goals and Topics

• The importance to clinical trials of a solid CTA
• We will discuss some key issues in negotiation and drafting
• From baseline questions to the current challenges
Definitions:

- **Research**
  
  45 CFR 46.102(d): “systematic investigation...designed to develop or contribute to generalizable knowledge” about human disease and healthcare.

- **Quality Improvement**
  
  *CMS Quality Improvement Organization Manual:*
  
  “an assessment of a patient care problem for the purpose of improving care through peer analysis, intervention, resolution of the problem and follow-up...[A] set of related activities designed to achieve measureable improvement in processes and outcomes of care.”
Common Characteristics

Both QI and research

- Ask clinically important questions
- Use patient data
- Apply statistical analysis to patient data
- Retrieve patient information from “the bedside”
- Aim to improve patient care
Differences

QI

• Is designed to bring about more immediate improvements in healthcare delivery
• Is designed to have its findings applicable only to the institution/organization
• Does not require fixed protocols (i.e., can adapt the project over time)
Overlap

When QI activities are designed to accomplish research purpose as well as improve quality of care for institution’s/organization’s patients

- May constitute non-exempt human subjects research that requires IRB review

  Example: Project involves introducing untested clinical intervention for purposes that include not only improving quality of care but also collecting patient outcomes information to establish scientific evidence to determine how well the intervention achieves its intended results

- Intent to publish, alone, is insufficient criterion to determine whether QI activity constitutes research
The CTA Baseline

• Who, what, where, when, why?
• This will tell you parties, subject matter, involved sites, the term and the purposes
• Translates to who needs to participate in the drafting, how the funds flow will work, who is responsible for monitoring what, and where must the controls, rights to review or audit, etc. be.
Who will do the drafting?

• It should not matter, provided the result is neutral and takes cognizance of the needs of each party.
  • For profit vs. Non-profit status
  • Disclosures in the public company environment

• The involved parties must be clearly identified and bound
  • Sponsor, site, PI, subcontractors
  • Potential for changes must be considered over time (e.g. PI movement)
  • How to address a situation where the PI is not employed by the site (e.g. private practice physician)

• Who will do the negotiating?
  • The marketing department vs. the R&D Group
  • You are only negotiating the CTA, not equipment purchases or employment relationship
You must end up with a Written Agreement Addressing--

• **Who pays for what**
  - FMV for all the services identified to avoid AKS and Stark problems
    - Can the vendor/sponsor pay for a non-profit’s attorneys fees?
    - Fitting into the AKS and Stark exceptions as appropriate
      - Personal services
      - Leases of equipment and space
  - **How will funds flow work - who pays who, when and for what?**
    - Payment in advance, in arrears, on milestone completion?
    - Paymaster control - through the site vs. direct payments to the PI
Special payment issues

• Institutional payment policies (acceptable vs. unacceptable examples)

• Mid-course corrections

• Responsibility for third party costs
Starting and stopping (term and termination) provisions

• What are all the termination events?
• What are appropriate payment considerations when a trial terminates prior to its completion date - recoupment of expenditures for capital and personnel
RESEARCH – RELATED INJURY ISSUES
Payment for Research – Related Injury/Illness

• Ethical and Practical Issues
  • Research principles in the Belmont Report* support providing compensation
    • Respect for Persons
    • Beneficence (minimize harms and maximize benefits)
    • Justice (Fair distribution of research benefits and burdens)

• **Practical problems:**
  • Financial consequences for research sites and sponsors
  • Determining causation of injury
    • “Substantial factor” test?
    • Use independent individual to determine causation?
    • Appeals process?
  • Identifying compensable “harms”
    • Emotional harm?
    • Long term care?
    • Pain and suffering? Lost wages? Punitive damages?
    • Monetary cap?
  • Exclude any of the following?
    • Pre-existing conditions
    • MD negligence, reckless misconduct
    • Institutional negligence, reckless misconduct
    • Injuries sustained by subjects who don’t follow instructions
• Legal Issues
  • For research involving more than minimal risk, federal regulations do require discussion regarding availability of compensation and treatments for research-related injuries; federal regulations do not require researchers, sponsors or research sites to offer payment for treatment of injuries. 45 CFR 46.116; 21 CFR 50.25
• Medicare Secondary Payer Issues
  • In general, Medicare is secondary to other insurers.
  • Does sponsor’s “promise to pay” for study-related injuries if insurance doesn’t cover make sponsor a primary payer?
  • 2004 CMS letter regarding application of MSP to clinical trial injury coverage in situation where sponsor agreed to pay for medically necessary services related to injuries resulting from research participation if these services were not otherwise covered by another payer.
    - The clinical trial sponsor’s agreement with trial participants that it will pay for medically necessary services related to injuries participants may receive as a result of participation in the trial constitutes a plan or policy of insurance under which payment can reasonably be expected to be made in the event such an injury occurs...Therefore, Medicare will not make payment if it is aware [of such a situation]
• Medicare, Medicaid and SCHIP Extension Act of 2007 (PL110-173, December 29, 2007, 121 Stat 2492)/HIPPA
  • As of July 1, 2009, Section 111 (8) requires liability insurance plans to take these steps when claim is filed against a plan or against an individual or entity insured or covered by the plan:
    – Identify whether claimant is Medicare beneficiary
    – If claimant is identified as Medicare beneficiary, report to CMS the identity of the beneficiary and other specified information required to enable coordination of benefits determination
  • May 26, 2010 CMS “Alert” reiterated that sponsor’s payments for research-related injury treatment costs must be reported pursuant to Section 111 of MMSEA
  • Do above requirements raise HIPPA concerns?

Note: unlikely that sponsor could shift reporting requirements to site in CTA
Practices

• Variability in CTAs regarding sponsor coverage in terms of:
  • Payment of subject vs. reimbursement of Institution for treating subject’s injury
  • Payment for only emergency treatment
  • Payment of Institution’s costs vs. fees
  • Payment secondary to private insurance coverage
• Fairness concerns when sponsors allowed to bill private insurers primary to their coverage
  • Imposes costs on subjects in form of co-payments, deductibles, increased premiums
  • Such costs may make participation financially impossible for some, creating bias against privately insured subjects (compared to Medicare beneficiaries and uninsured, who are not required to pay these costs)
ACCESS TO AND USE OF STUDY RECORDS
Sponsor’s access to Institution’s records

- Sponsor’s perspective: Needs access to all study-related documents
  - Needs to assure research conducted in compliance with regulations
  - Best positioned to respond to FDA audits, inspections, and would need such access in that event; FDA inspections, audits could compromise completion of study
  - Wants to help institution
• Institution’s perspective: sponsor’s access should be limited
  • Needs to comply with HIPPA/state confidentiality laws
    • Sponsor’s access delineated in HIPPA authorization often is not unlimited
  • Sponsor has no need to see records/be involved in investigations/audits not related to the specific study
  • Institution must be free to respond to regulatory authorities without approval by sponsor
Common ground

- Institution permits sponsor to examine and audit all study-related records and reports, in accordance with applicable privacy laws and regulations
- Institution agrees to notify sponsor in the event that the FDA or other regulatory authority notifies Institution of a pending inspection/audit related to the study or that would affect the Institution’s ability to conduct the study
- Institution agrees to take such action necessary to address any study-related deficiencies noted in audit, after giving sponsor an opportunity to comment
• Institution’s access to Study Data and Results from other sites
  • Institution’s perspective:
    • Safety information must be disclosed
    • Knowledge obtained from the research should be shared even if knowledge is that the intervention does not work
  • Sponsor’s perspective:
    • Need to protect proprietary information
    • Need to process all of the data
    • Need for quality control
Intellectual property access and ownership

• An IP assessment
  • Whose IP is being used for what
  • What IP could potentially be created

• Potential scenarios
  • The “Eureka moment”
  • Addressing the private medical staff - hospital site challenge
  • The disclosure obligation
  • Ownership of physical/tangible property and the intangible (slides, tissue, software, film, etc.)
  • The obligation to make disclosures under each scenario and how to address them
Ownership allocation

- Measuring respective contribution or allocation by agreement prospectively
- Each party has a royalty free license for their own (internal research) uses
- The responsibility for development
  - Patent prosecution and its expenses
  - Reversion if no development within fixed time
  - Notice of abandonment and the right to assume the process
Liability, Indemnity and Insurance

• What are we trying to accomplish?
  • Responsibility matches the creation of risk
  • Who created the protocol/who implements the protocol
• The boilerplate often does not line up with this
Indemnity and insurance follow

• The full scope of the risk
• Limitations issues
  • Exposure not limited to fees paid
  • Liability for collateral exposure (indirect, consequential, etc., damages)
  • What about exclusions for “simple” negligence? Does this make sense?
• Dispute resolution
  • Check with carrier!
  • Arbitration vs. litigation
Sponsor’s goals, concerns

- Overall goals:
  - Generate data, properly complete the study
  - Obtain marketing approval
  - Protect IP via patents

- Publication goals:
  - Validate scientific basis for intervention
  - Information for investment community
Institution’s goals, concerns

- Free scholarly exchange (good and bad results) and the expansion of ideas
- Scholarly publication, professional development
- Advance science and improve public health
- Generate IP and new avenues for research
- Compliance with registration requirements
- Maintenance of tax exempt status
Post trial licenses

• Most agreements also address this potential
• Often in the form of an exclusive option to negotiate for a defined period
• There are special issues for tax exempt financed facilities
Variations in CTA

- Type of publications allowed, addressed (articles in peer reviewed journal, abstract submissions, posters, oral presentations, posting to www.clinicaltrials.gov)
- Sponsor review times (e.g., expedited times for poster presentations and abstracts)
- Restrictions to publishing (e.g., sponsor right to request deletion of Sponsor confidential information, not results; additional delay 40-60 days to protect IP/file patent application)
External disclosure issues

• Dr. Arrested on Insider Charges Over Clinical Trial Data and Faces SEC Suit - November 2, 2010
• “ Former Drug Executive Convicted of Wire Fraud” - N.Y. Times, September 29, 2009
  • Overemphasis on positive news in a trial that did not meet endpoints
• Twinde v. Threshold Pharmaceuticals (N.D. Cal. 2009) (Order, Motion to Dismiss)
  • Securities class action
  • Promoting a drug despite indications not likely to pass FDA approval
  • Alleged misleading information about status and future intentions regarding Clinical Trials
  • Adequate allegations of material misrepresentation in the Press Release and Quarterly report based on failure to disclose evidence of liver toxicity in ongoing clinical trials
In re Entropin Securities Litigation (C. D. Cal. 2007) (Order, Motions for SJ)

• Facts are material if substantial likelihood reasonable investor would consider important (10-b-5 standard)
• Issue of fact existed as to whether a trial was a truly double blind study
• Issue of fact existed with respect to data selection and manipulation (“...in order to select a self-serving subset of analysis to be highlighted in the study report...”)

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Conclusion

• CTAs require understanding, thought, legal work
• Boilerplates (or master agreements) are not to be accepted at face value
• Consider changing circumstances over the life of trials/relationships
Questions?