

**Managing Regulatory Compliance for Investigator-
Initiated Research:**

**Interactions Among Industry, Sponsor-
Investigators, and Institutions**

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Agenda

1. Background
 - Why IITs?
 - Types of Industry Support
2. Regulatory Concerns
3. Industry Policies and Procedures
4. Contracting

Why IITs?

- Why does industry support IITs?
 - o Benefit to the company
 - New ideas
 - Less expensive way to obtain valuable data
 - o To advance medical and scientific knowledge of disease state
 - o Benefit to a patient population
 - o Fewer administrative obligations



Why IITs?

- Importantly, industry and the investigator/sponsor have mutual goals:
 - o Good research that results in publications, mutual benefits
 - o Good partnerships and continuing relationships
 - o Protecting human subjects
 - o Regulatory compliance



Types of Industry Support

- Possible funding sources for IITs
 - o Industry (my focus here)
 - o Government (e.g., NIH)
 - o Institution
 - o Non-profits
 - o Some combination of the above
- Types of industry support
 - o Monetary
 - o Product
 - o Publication planning
 - o Ideas/IP
 - o Some combination of the above



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Food & Drug Administration

- Increasing focus on clinical trials generally
- For example:
 - o Proposed Rule - Reporting Information Regarding Falsification of Data (Feb. 2010)
 - o IRB Continuing Review After Clinical Investigation Approval - Draft Guidance (Jan. 2010)
 - o Proposed rule - addition of an informed consent required element to 21 CFR 50.25 (Dec. 2009)
 - o Investigator Responsibilities — Protecting the Rights, Safety, and Welfare of Study Subjects (Oct. 2009)
 - o Final Rules on Access to Investigational Drugs (Aug. 2009)
 - o FDA Enhances Speed and Transparency of Actions Taken Against Misconduct in Drug and Device Development (Aug. 2009)
 - o FDA, European Medicines Agency Launch Good Clinical Practices Initiative (Aug. 2009)
 - o Frequently Asked Questions - IRB Registration (July 2009)



"Fraud and Abuse"

- **OIG Compliance Program Guidance**
 - o Is any purpose of a financial relationship intended to reward or induce referrals or recommendations of business payable under a federally-funded program?
 - o Concern that funding research conducted by customers can be used to induce or reward purchase of sponsor's products
 - o Post-marketing research particularly suspect, due to greater perception that the objective is to generate sales
 - o Insulate research grant making from sales and marketing function



“Fraud and Abuse”

• **AdvaMed Code on Interactions With Health Care Professionals**

- Research grants
 - “Support independent medical research with scientific merit”
 - Well-defined objectives and milestones
 - Not linked to purchase of products
- Consulting agreements
 - Written signed agreement specifying services to be performed (purpose of the research funding must be clearly documented)
 - Written research protocol
 - Compensation consistent with FMV
 - Need for the research based on legitimate criteria established in advance
- Selection based on qualifications and expertise



“Fraud and Abuse”

– **PhRMA Code on Interactions With Health Care Professionals**

Research should be conducted under a consulting arrangement that includes

- Written contract
- Legitimate need for the research identified in advance
- Defined selection criteria
- A reasonable number of researchers
- Documentation of work performed
- Compliance with meeting requirements (venue, etc)



Enforcement Examples

- Blackstone Medical (Dec. 2008)
 - o Whistleblower complaint alleging kickbacks to doctors to induce them to use company products
 - o Complaint was filed by a former regional manager and a former independent distributor
 - o Alleged kickbacks included sham consulting arrangements and research grants
- Schering Plough (Aug. 2006)
 - o Off-label marketing; illegal remuneration
 - o Awarding clinical studies based on volume of prescribing
 - o Also advisory boards that existed to provide stipends and entertainment to doctors



Enforcement Examples

- Neurontin (Warner Lambert; May 2004; \$430M)
 - o Plan to promote drug for off-label use that included research grant program intended to familiarize providers with use of drug in off-label situations
 - o Several other problematic activities
- Hoffman-LaRoche (1994)
 - o Grant program to enable physicians to study company product
 - o Program lacked scientific value
 - o Selected investigators for ability to recommend product, rather than ability to conduct study



Regulatory Concerns

- Bottom lines ...
 - o No intent to promote use or purchase of products
 - o No promotion of off-label use
 - Note: This does not necessarily exclude research on off-label uses
 - o No improper benefit to providers
 - o Separation from sales and marketing functions



Regulatory Concerns

- Bottom lines ...
 - o Industry supporters can (and should) be concerned about the right “paper trail”
 - o For example:
 - Legitimate work being done
 - Payments being made
 - Conflict of interests avoided



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Industry Policies & Procedures

- The past
 - o Primary channels for IITs were sales reps and/or medical sales liaisons
 - o For example, a survey conducted in 2006 indicated:
 - ~1/3 of pharma/biotech companies did not have an established process for tracking IITs*
 - ~ 1/2 did not have an IIT management dept*

**Medical News Today (Aug 10, 2006 and Sept 9, 2006)*



Industry Policies & Procedures

- Formalized processes increasingly common
- Adds uniformity and formality to process
- Driven by:
 - o Regulatory concerns
 - o Necessity borne by complex, global companies
 - o Economy?



Industry Policies & Procedures

- Program goals including establishing and evidencing:
 - o Intent
 - o That investigator is the sponsor
 - o FMV
 - o Controls to eliminate improper company influence
 - Separation of sales and marketing
 - Transparency/disclosure
 - Company role in the research



Industry Policies & Procedures

- Common elements designed to achieve these goals
 - o Standard requirements for a proposal
 - o Funneling proposals into a common repository
 - o Review by an established committee comprised of medical/R&D personnel
 - o Criteria for approval
 - o Standardization of support
 - o Contractual requirements



Industry Policies & Procedures

- Some company policies/programs also require the company to have a certain role in the research.
- For example:
 - o Monitoring
 - o Training
 - o Sharing data/providing reports
 - o Company review/input on protocol



Industry Policies & Procedures

- However, in practice, these programs can take many forms
- Examples:
 - o Company policy on how to handle study ideas proposed to sales reps
 - o Globally integrated online submission program
 - o Processes organized by therapeutic area
 - o Processes organized by geographic region (e.g., US v. ex-US)



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Investigator-Initiated Study Agreements

- Key purposes of the agreement
 - o Establish rights and responsibilities
 - o Set forth site/PI and company roles
 - o Protect both parties from a regulatory standpoint
- More variation in these agreements than in research agreements where company is the sponsor



Investigator-Initiated Study Agreements

- **Compliance with Laws**
 - o Clearly specific who is the “sponsor” from a regulatory perspective
 - o Sponsor (i.e., PI and/or site, if site is contracting on PI behalf) must comply with applicable laws and regulations
 - o From industry perspective, helps ensure company can use data in FDA applications, if needed/desired



Investigator-Initiated Study Agreements

– **Publication**

- o Typically more liberal publication rights for PI, although company may still review (and perhaps comment) and postpone for certain reasons
- o Memorialize that PI is “responsible party” for clinicaltrials.gov purposes

– **Confidentiality**

- o May or may not be mutual – companies often consider their interests in the study, what information they actually provide, and desired use of data and results
- o Ex: Does the company want the ability to use the data in marketing submissions or otherwise?
- o Ex: Is the company supplying proprietary data to help develop study, or was idea completely the investigator’s?



Investigator-Initiated Study Agreements

– **Audit/monitoring rights**

- o PI is the sponsor and is therefore responsible for monitoring from a regulatory standpoint
- o Company may require audit/monitoring rights, depending upon level of company’s involvement

– **Adverse event reporting**

- o Again, PI is the sponsor and responsible for regulatory obligations
- o However, agreement typically requires site/PI to submit AEs to company
- o In post-market context, company may be required to submit AEs if they are involved in the study



Investigator-Initiated Study Agreements

– **Data ownership**

- o Site/PI typically owns data, but provides company with
 - Periodic and final reports
 - Data license

– **Intellectual Property**

- o PI/site often owns inventions, except perhaps inventions directly relating to company product
- o Ask for license
- o Potential limits on ownership rights under U.S. law if federal funding



Investigator-Initiated Study Agreements

– **Indemnification**

- o Typically far more limited than in a regular CTA, but depends on company involvement with study
- o Ex: harms directly caused by company product (manufacturing defects/product liability); company use of study data

– **Subject injury**

- o Varies
 - No company reimbursement v.
 - Injuries directly caused by problem with company product (similar to indemnification) v.
 - More broad, if company more involved with study



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Questions and Discussion

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